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<p>(21) International Application Number: PCT/US00/11845</p> <p>(22) International Filing Date: 1 May 2000 (01.05.00)</p> <p>(30) Priority Data:</p> <table> <tr> <td>60/198,249</td> <td>4 May 1999 (04.05.99)</td> <td>US</td> </tr> <tr> <td>09/552,355</td> <td>19 April 2000 (19.04.00)</td> <td>US</td> </tr> </table> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application</p> <table> <tr> <td>US</td> <td>09/552,355 (CON)</td> </tr> <tr> <td>Filed on</td> <td>19 April 2000 (19.04.00)</td> </tr> </table> <p>(71) Applicants (for all designated States except US): AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Girardia Farms, Madison, NJ 07840 (US). LIGAND PHARMACEUTICALS, INC. [US/US]; 10275 Science Center Drive, San Diego, CA 92121 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): GRUBB, Gary, S. [US/US]; 825 Briarwood Road, Newtown Square, PA 19073 (US). ZHI, Lin [CN/US]; 7794 Roan Road, San</p>		60/198,249	4 May 1999 (04.05.99)	US	09/552,355	19 April 2000 (19.04.00)	US	US	09/552,355 (CON)	Filed on	19 April 2000 (19.04.00)	<p>Diego, CA 92129 (US). JONES, Todd, K. [US/US]; 546 Marview Drive, Solana Beach, CA 92075 (US). MARSCHKE, Keith, B. [US/US]; 12565 Escala Drive, San Diego, CA 92128 (US). TEGLEY, Christopher, M. [US/US]; 478 Thunderhead Street, Thousand Oaks, CA 91360 (US).</p> <p>(74) Agents: KODROFF, Cathy, A. et al.; Howson and Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US).</p> <p>(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p>
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<p>(54) Title: COMPOSITIONS CONTAINING BENZIMIDAZOLONES AND PROGESTOGENS</p>												
<p style="text-align: center;"> (1) </p>												
<p>(57) Abstract</p> <p>This invention relates to cyclic combination therapies and regimens utilizing substituted indoline derivative compounds which are antagonists of the progesterone receptor having general structure (1) wherein: A is O, S, or NR⁴; B is a bond between A and C=Q, or the moiety CR⁵R⁶; R⁴, R⁵, R⁶ are independently selected from H or optionally substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, or heterocyclic groups, or cyclic alkyl constructed by fusing R⁴ and R⁵ to form a 5 to 7 membered ring; R¹ is selected from H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkynyl, alkynyl, -COH, or optionally substituted alkynyl, -COH, or optionally substituted -CO(C₁ to C₃ alkyl), -CO(aryl), -CO(C₁ to C₃ alkoxy), or -CO(C₁ to C₃ aminoalkyl) groups; R² is selected from H, halogen, CN, NO₂, or optionally substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, or C₁ to C₆ aminoalkyl groups; R³ is selected from a trisubstituted benzene ring; or a 5- or 6-membered heteroaromatic ring containing 1 or 2 substituents; or a pharmaceutically acceptable salt thereof, in combination with a progestational agent, an estrogen, or both or for the treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate. These combinations may also be used in methods of contraception, to stimulate food intake or for minimization of side effects or cyclic menstrual bleeding.</p>												

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COMPOSITIONS CONTAINING BENZIMIDAZOLONES AND PROGESTOGENS

Field of the Invention

This invention relates to regimens of administering compounds which are
5 antagonists of the progesterone receptor.

Background of the Invention

Intracellular receptors (IR) form a class of structurally related gene regulators known as "ligand dependent transcription factors" (R. M. Evans, *Science*, **240**, 889, 10 1988). The steroid receptor family is a subset of the IR family, including progesterone receptor (PR), estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR).

The natural hormone, or ligand, for the PR is the steroid progesterone, but synthetic compounds, such as medroxyprogesterone acetate or levonorgestrel, have 15 been made which also serve as ligands. Once a ligand is present in the fluid surrounding a cell, it passes through the membrane *via* passive diffusion, and binds to the IR to create a receptor/ligand complex. This complex binds to specific gene promoters present in the cell's DNA. Once bound to the DNA the complex modulates the production of mRNA and protein encoded by that gene.

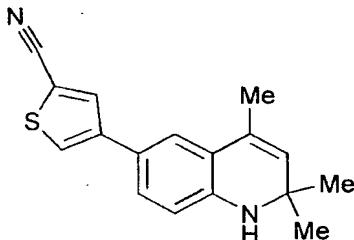
20 A compound that binds to an IR and mimics the action of the natural hormone is termed an agonist, whilst a compound which inhibits the effect of the hormone is an antagonist.

PR agonists (natural and synthetic) are known to play an important role in the 25 health of women. PR agonists are used in birth control formulations, typically in the presence of an ER agonist. ER agonists are used to treat the symptoms of menopause, but have been associated with a proliferative effect on the uterus which can lead to an increased risk of uterine cancers. Co-administration of a PR agonist reduces/ablates that risk.

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PR antagonists may also be used in contraception. In this context they may be administered alone (Ulmann, et al, *Ann. N.Y. Acad. Sci.*, **261**, 248, 1995), in combination with a PR agonist (Kekkonen, et al, *Fertility and Sterility*, **60**, 610, 1993) or in combination with a partial ER antagonist such as tamoxifen (WO 96/19997 A1 5 July 4, 1996). PR antagonists may also be useful for the treatment of hormone dependent breast cancers (Horwitz, et al, *Horm. Cancer*, 283, pub: Birkhaeuser, Boston, Mass., ed. Vedeckis) as well as uterine and ovarian cancers. PR antagonists may also be useful for the treatment of non-malignant chronic conditions such as fibroids (Murphy, et al, *J. Clin. Endo. Metab.*, **76**, 513, 1993) and endometriosis 10 (Kettel, et al, *Fertility and Sterility*, **56**, 402, 1991). PR antagonists may also be useful in hormone replacement therapy for post menopausal patients in combination with a partial ER antagonist such as tamoxifen (U.S. Patent No. 5,719,136). PR antagonists, such as mifepristone and onapristone, have been shown to be effective in a model of hormone dependent prostate cancer, which may indicate their utility in the treatment of 15 this condition in men (Michna, et al, *Ann. N.Y. Acad. Sci.*, **761**, 224, 1995).

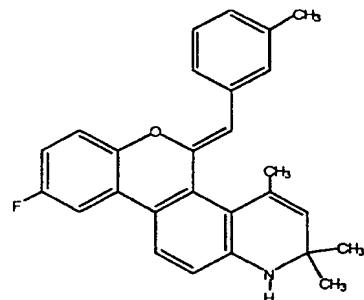
Jones, et al, (U.S. Patent No. 5,688,810) disclose the PR antagonist dihydroquinoline 1.



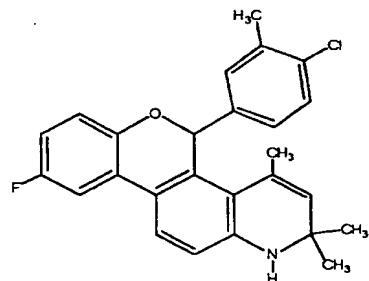
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20 Jones, et al, described the enol ether 2 (U.S. Patent No. 5,693,646) as a PR ligand.

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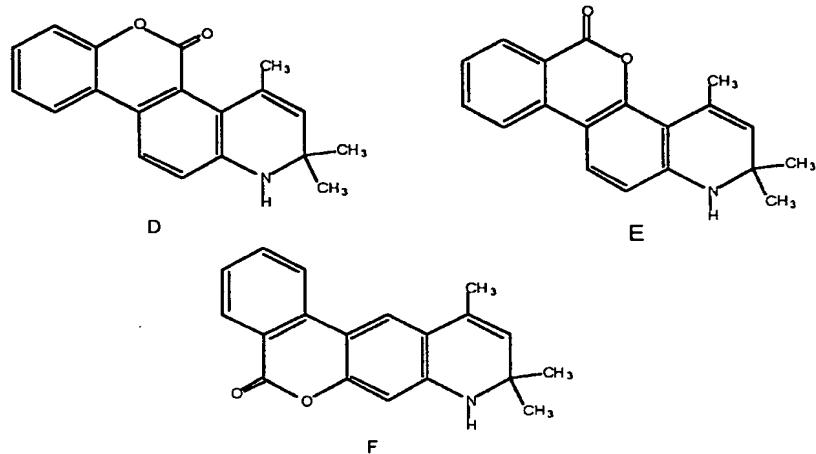
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Jones, *et al*, described compound 3 (U.S. Patent No. 5,696,127) as a PR
5 ligand.

**3**

Zhi, *et al*, described lactones 4, 5 and 6 as PR antagonists (J. Med. Chem., 41,
10 291, 1998).

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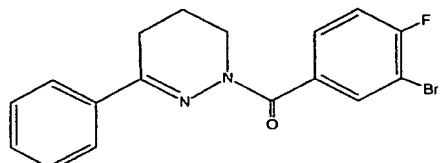


Zhi, *et al.*, described the ether 7 as a PR antagonist (*J. Med. Chem.*, **41**, 291, 1998).

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Combs, *et al.*, disclosed the amide 8 as a ligand for the PR (*J. Med. Chem.*, **38**, 4880, 1995).

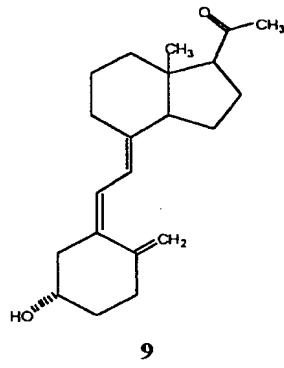


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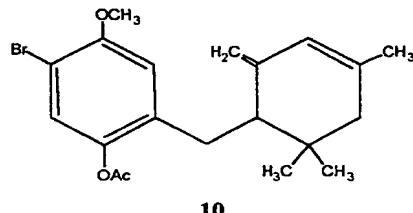
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Perlman, *et. al.*, described the vitamin D analog **9** as a PR ligand (*Tet. Letters*, **35**, 2295, 1994).



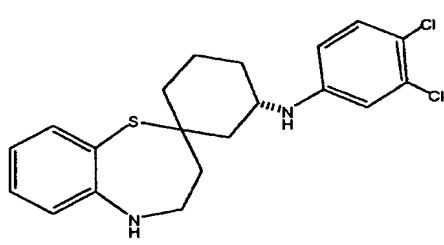
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Hamann, *et al.*, described the PR antagonist **10** (*Ann. N.Y. Acad. Sci.*, **761**, 383, 1995).

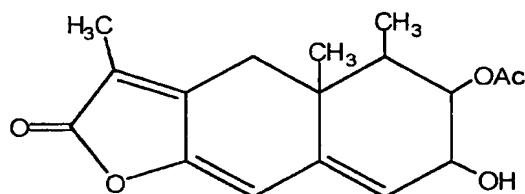


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Chen, et al, described the PR antagonist **11** (Chen, et al, POI-37, 16th Int. Cong. Het. Chem. Montana, 1997)



Kurihara, *et. al.*, described the PR ligand **12** (*J. Antibiotics*, **50**, 360, 1997).

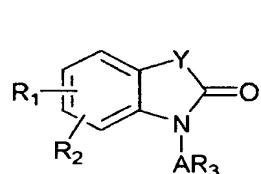


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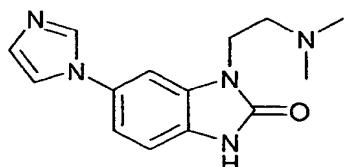
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Among the examples of the prior art, Ueda et al. (EP 22317) claimed benzothiazoline and benzoxazoline compounds of formula **A** as the inhibitors of aldose reductase. The benzimidazolinone derivatives such as compound **B** were disclosed by 10 Hara et al. (EP 454330) and claimed as lung surfactant secretion promoters. In their preparation of benzoimidazole and analogues as antiulcer and cardiovascular agents, Bru-Magniez et al. (EP 385850) synthesized the benzoimidazolinones such as compound **C**. Used as cAMP PDE III inhibitors, benzoimidazolinones, benzoxazolinones, and benzothiazolinones as shown in formula **D** were reported by 15 Singh et al (*J. Med. Chem.*, **37**, 248-254 (1994).).

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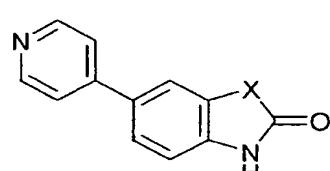
A



B



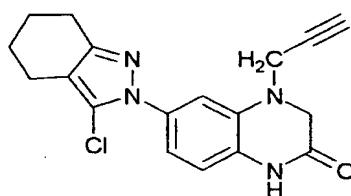
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D (X = NH, O, S)

Related to quinoxalin-2-ones, European patent (Ganzer et al. EP 311135) discloses the compounds such as **E** as herbicides.

5



E

U.S Patent No. 5,521,166 (Grubb) teaches cyclophasic hormonal regimens comprising an antiprogestin and a progestin wherein the progestin is administered in the alternating presence and absence of an antiprogestin. The disclosed regimens also provide for use of an estrogen for a period of from 2-4 days to prevent breakthrough bleeding.

Description of the Invention

This invention provides combination therapies and dosing regimens utilizing antiprogestational agents in combination with one or more progestational agents. This invention further provides methods of treatment and dosing regimens further utilizing in combination with these antiprogestins and progestins, an estrogen, such as ethinyl estradiol.

These regimens and combinations may be administered to a mammal to induce contraception or for the treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate. Additional uses of the invention include stimulation of food intake. The uses herein for the treatment and/or prevention of the conditions or diseases described above includes the continuous administration or periodic discontinuation of administration of the invention to allow for minimization of effect dose or minimization of side effects or cyclic menstrual bleeding.

The use of this invention for contraception includes administration, preferably orally, to a female of child bearing age an antiprogestin in combination with an estrogen or progestin or both. These administration regimens are preferably carried out over 28 consecutive days, with a terminal portion of the cycle containing administration of no progestins, estrogens or anti-progestins.

The progestins of these combinations may be administered alone or in combination with an estrogen for the first 14 to 24 days of the cycle, the progestins being administered at a dosage range equal in progestational activity to about 35 μ g to about 150 μ g levonorgestrel per day, preferably equal in activity to from about 35 μ g to about 100 μ g levonorgestrel per day. An antiprogestin may then be administered alone or in combination with an estrogen for a period of 1 to 11 days to begin on any cycle day between day 14 and 24. The anti-progestin in these combinations may be administered at a dose of from about 2 μ g to about 50 μ g per day and the estrogen may be administered at a dose of from about 10 μ g to about 35 μ g per day. In an oral

administration, a package or kit containing 28 tablets will include a placebo tablet on those days when the antiprogestin or progestin or estrogen is not administered.

In a preferred embodiment of this invention, the progestins of this invention may be administered alone or in combination with estrogen for the initial 18 to 21 days 5 of a 28-day cycle, followed by administration of an antiprogestin, alone or in combination with an estrogen, for from 1 to 7 days.

The estrogen to be used in the combinations and formulations of this invention is preferably ethinyl estradiol.

Progestational agents useful with this invention include, but are not limited to, 10 levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, nomegestrol, or (17-deacetyl)norgestimate. Among the preferred progestins for use in the combinations of this invention are levonorgestrel, gestodene and trimegestone.

15 Examples of orally administered regimens of this invention over a 28 day cycle include administration of a progestational agent solely for the first 21 days at a daily dose equal in progestational activity to from about 35 to about 100 µg of levonorgestrel. An antiprogestin compound of this invention may then be administered at a daily dose of from about 2 to 50 mg from day 22 to day 24, followed by no 20 administration or administration of a placebo for days 25 to 28. It is most preferred that the daily dosages of each relevant active ingredient be incorporated into a combined, single daily dosage unit, totaling 28 daily units per 28-day cycle.

In another regimen, a progestational agent may be coadministered for the first 21 days at a daily dose equal in progestational activity to from about 35 to about 150 25 µg levonorgestrel, preferably equal in activity to from about 35 to about 100 µg levonorgestrel, with an estrogen, such as ethinyl estradiol, at a daily dose range of from about 10 to about 35 µg. This may be followed as described above with an antiprogestin administered at a daily dose of from about 2 to 50 mg from day 22 to day 24, followed by no administration or administration of a placebo for days 25 to 28.

- 10 -

Still another regimen within the scope of this invention will include coadministration from days 1 to 21 of a progestational agent, the progestational agent, preferably levonorgestrel, being administered at a daily dose equal in progestational activity to from about 35 to about 100 µg levonorgestrel, and an estrogen, such as 5 ethinyl estradiol, at a daily dose range of from about 10 to about 35 µg. This will be followed on days 22 to 24 by coadministration of an antiprogestin (2 to 50 mg/day) and an estrogen, such as ethinyl estradiol, at a daily dose of from about 10 to about 35 µg. From day 25 to day 28, this regimen may be followed by no administration or administration of a placebo.

10 This invention also kits or packages of pharmaceutical formulations designed for use in the regimens described herein. These kits are preferably designed for daily oral administration over a 28-day cycle, preferably for one oral administration per day, and organized so as to indicate a single oral formulation or combination of oral formulations to be taken on each day of the 28-day cycle. Preferably each kit will 15 include oral tablets to be taken on each the days specified, preferably one oral tablet will contain each of the combined daily dosages indicated.

According to the regimens described above, one 28-day kit may comprise:

- a) an initial phase of from 14 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg 20 levonorgestrel, preferably equal in progestational activity to about 35 to about 100 µg levonorgestrel;
- b) a second phase of from 1 to 11 daily dosage units of an antiprogestin compound of this invention, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and
- 25 c) optionally, a third phase of an orally and pharmaceutically acceptable placebo for the remaining days of the cycle in which no antiprogestin, progestin or estrogen is administered.

A preferred embodiment of this kit may comprise:

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a) an initial phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal in progestational activity to about 35 to about 100 µg levonorgestrel;

5 b) a second phase of 3 daily dosage units for days 22 to 24 of an antiprogestin compound of this invention, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

 c) optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

Another 28-day cycle packaging regimen or kit of this invention comprises:

10 a) a first phase of from 18 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal in activity to from about 35 to about 100 µg levonorgestrel, and, as an estrogen, ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and

15 b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of this invention at a daily dose of from about 2 to 50 mg; and

 c) optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0-9 days in the 28-day cycle in which no progestational agent, estrogen or antiprogestin is administered.

A preferred embodiment of the kit described above may comprise:

20 a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal in activity to from about 35 to about 100 µg levonorgestrel, and, as an estrogen, ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and

25 b) a second phase of 3 daily dosage units for days 22 to 24 of an antiprogestin administered at a daily dose of from about 2 to 50 mg; and

 c) optionally, a third phase of 4 daily dose units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

A further 28-day packaged regimen or kit of this invention comprises:

- 12 -

a) a first phase of from 18 to 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 µg levonorgestrel, preferably equal in activity to from about 35 to about 100 µg levonorgestrel, and ethinyl estradiol at a daily dose range of from 5 about 10 to about 35 µg;

b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of this invention at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and

c) optionally, an orally and pharmaceutically acceptable placebo for 10 each of the remaining 0-9 days in the 28-day cycle in which no progestational agent, estrogen or antiprogestin is administered.

A preferred embodiment of the package or kit just described comprises:

a) a first phase of 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to 15 about 35 to about 150 µg levonorgestrel, preferably from about 35 to about 100 µg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg;

b) a second phase of 3 daily dose units for days 22 to 24, each dose unit containing an antiprogestin of this invention at a concentration of from 2 to 50 mg; and 20 ethinyl estradiol at a concentration of from about 10 to about 35 µg; and

c) optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

In each of the regimens and kits just described, it is preferred that the daily dosage of each pharmaceutically active component of the regimen remain fixed in each 25 particular phase in which it is administered. It is also understood that the daily dose units described are to be administered in the order described, with the first phase followed in order by the second and third phases. To help facilitate compliance with each regimen, it is also preferred that the kits contain the placebo described for the final days of the cycle. It is further preferred that each package or kit comprise a

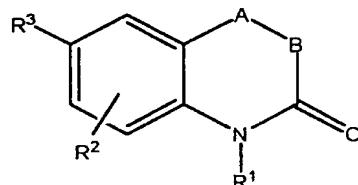
pharmaceutically acceptable package having indicators for each day of the 28-day cycle, such as a labeled blister package or dial dispenser packages known in the art.

In this disclosure, the terms anti-progestational agents, anti-progestins and progesterone receptor antagonists are understood to be synonymous. Similarly, 5 progestins, progestational agents and progesterone receptor agonists are understood to refer to compounds of the same activity.

These dosage regimens may be adjusted to provide the optimal therapeutic response. For example, several divided doses of each component may be administered daily or the dose may be proportionally increased or reduced as indicated by the 10 exigencies of the therapeutic situation. In the descriptions herein, reference to a daily dosage unit may also include divided units which are administered over the course of each day of the cycle contemplated.

Compounds of this invention which may be used as the anti-progestational agents in the kits, methods and regimens herein are those of the Formula 1:

15



wherein:

A is O, S, or NR⁴;

B is a bond between A and C=Q, or the moiety CR⁵R⁶;

20 R⁴, R⁵, R⁶ are independently selected from H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, cyclic alkyl constructed by fusing R⁴ and R⁵ to from a 5 to 7 membered ring;

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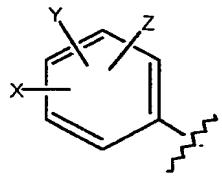
R^1 is selected from H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, alkynyl, substituted alkynyl, or COR^A;

R^A is selected from H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^2 is selected from H, halogen, CN, NO₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, or substituted C₁ to C₆ aminoalkyl;

R^3 is selected from a) or b):

10 a) R^3 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



15 X is selected from the group of halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^B, OCOR^B, or NR^CCOR^B;

20 R^B is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^C is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkoxy; or

- 15 -

b) R^3 is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO₂ or NR⁷ and containing one or two independent substituents from the group of H, halogen, CN, NO₂ and C₁ to C₃ alkyl, C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, COR^D, or NR^ECOR^D;

5 R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

R^7 is H, or C₁ to C₃ alkyl;

10 or a pharmaceutically acceptable salt thereof.

Preferred anti-progestational compounds of this invention include those of the general formula described above wherein:

A is O, S, or NR⁴;

B is a bond between A and C=Q, or the moiety CR⁵R⁶;

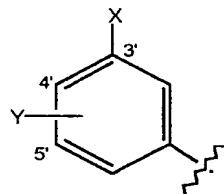
15 R⁴, R⁵, R⁶ are independent substituents from the group including H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, or cyclic alkyl constructed by fusing R⁴ and R⁵ to from a 5 to 7 membered ring;

20 R¹ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, or COR^A;

R^A is H, C₁ to C₄ alkyl, C₁ to C₄ alkoxy;

R² is H, halogen, NO₂, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

R³ is a disubstituted benzene ring containing the substituents X and Y as shown below

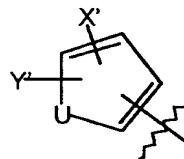


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X is taken from the group of halogen, CN, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, or C₁ to C₃ thioalkoxy;

Y is a substituent on the 4' or 5' position from the group of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₄ alkyl, or C₁ to C₃ thioalkoxy;
5 or

R³ is a five membered ring with the structure:



wherein:

10 U is O, S, or NR⁷;

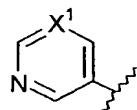
R⁷ is H, C₁ to C₃ alkyl, or C₁ to C₄ CO₂alkyl;

X' is selected from the group of halogen, CN, NO₂, C₁ to C₃ alkyl or C₁ to C₃ alkoxy;

Y' is H or C₁ to C₄ alkyl;

15 or

R³ is a six membered ring with the structure:



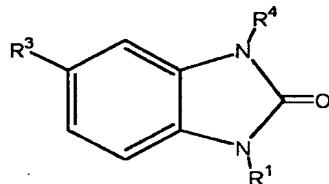
X¹ is N or CX²;

X² is halogen, CN or NO₂;

20

or a pharmaceutically acceptable salt thereof.

Another preferred progesterone receptor antagonist subgroup of this invention comprises compounds of the general formula:



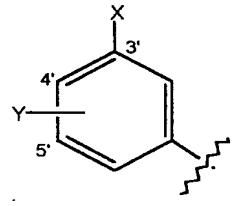
wherein:

R¹ is selected from H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, alkynyl, substituted alkynyl, or COR^A;

5 R^A is selected from H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

10 R⁴ is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, benzyl, or substituted benzyl; and

R³ is selected from halogen or a disubstituted benzene ring containing the substituents X and Y as shown below



15 X is taken from the group of halogen, CN, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, NO₂, C₁ to C₃ perfluoroalkyl, or C₁ to C₃ thioalkoxy;

Y is a substituent on the 4' or 5' position from the group of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₄ alkyl, or C₁ to C₃ thioalkoxy; or a pharmaceutically acceptable salt thereof.

20 The anti-progestational compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and

diastereomers. While shown without respect to stereochemistry in Formula I, II, and III, the present invention includes such optical isomers and diastereomers of these compounds; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and 5 pharmaceutically acceptable salts thereof.

The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having one to eight carbon atoms, preferably one to six carbon atoms; "alkenyl" is intended to include both straight- and branched-chain alkyl group with at least one carbon-carbon double bond and two to eight carbon 10 atoms, preferably two to six carbon atoms; "alkynyl" group is intended to cover both straight- and branched-chain alkyl group with at least one carbon-carbon triple bond and two to eight carbon atoms, preferably two to six carbon atoms.

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl as just described having one or more substituents 15 from the group including halogen, CN, OH, NO₂, amino, aryl, heterocyclic, substituted aryl, substituted heterocyclic, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, arylthio. These substituents may be attached to any carbon of alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

20 The term "aryl" is used herein to refer to an aromatic system which may be a single ring or multiple aromatic rings fused or linked together as such that at least one part of the fused or linked rings forms the conjugated aromatic system. The aryl groups include but not limited to phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, phenanthryl. The term "substituted aryl" refers to aryl as just 25 defined having one to four substituents from the group including halogen, CN, OH, NO₂, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio. The term "heterocyclic" is used herein to describe a stable 4- to 7-membered monocyclic or a stable multicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated, and which

consists of carbon atoms and from one to four heteroatoms selected from the group including N, O, and S atoms. The N and S atoms may be oxidized. The heterocyclic ring also includes any multicyclic ring in which any of above defined heterocyclic rings is fused to an aryl ring. The heterocyclic ring may be attached at any heteroatom or

5 carbon atom provided the resultant structure is chemically stable. Such heterocyclic groups include, for example, tetrahydrofuran, piperidinyl, piperazinyl, 2-oxopiperidinyl, azepinyl, pyrrolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, indolyl, quinolinyl, thienyl, furyl, benzofuranyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and

10 isoquinolinyl. The term "substituted heterocyclic" is used herein to describe the heterocyclic just defined having one to four substituents selected from the group which includes halogen, CN, OH, NO₂, amino, alkyl, substituted alkyl, cycloalkyl, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

15 The term "alkoxy" is used herein to refer to the OR group, where R is alkyl or substituted alkyl. The term "aryloxy" is used herein to refer to the OR group, where R is aryl or substituted aryl. The term "alkylcarbonyl" is used herein to refer to the RCO group, where R is alkyl or substituted alkyl. The term "alkylcarboxy" is used herein to refer to the COOR group, where R is alkyl or substituted alkyl. The term

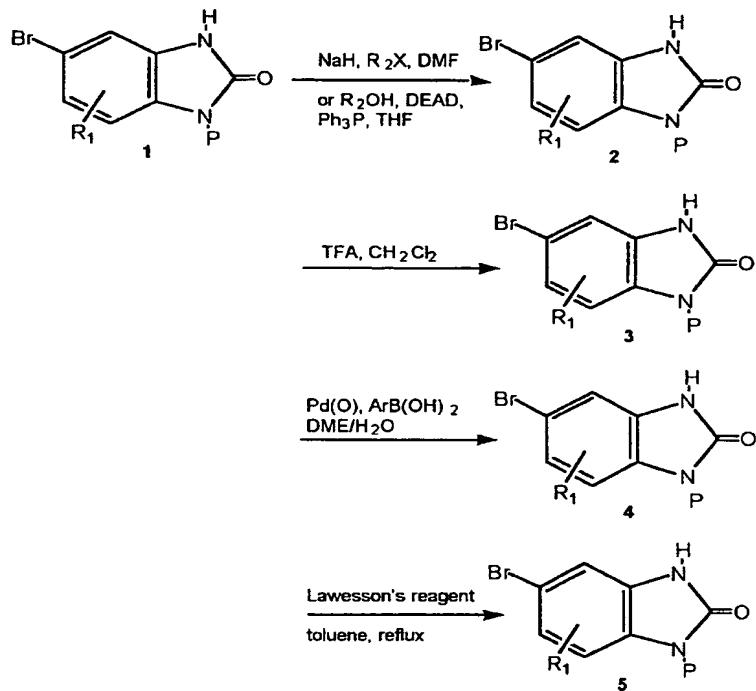
20 "aminoalkyl" refers to both secondary and tertiary amines wherein the alkyl or substituted alkyl groups, containing one to eight carbon atoms, which may be either same or different and the point of attachment is on the nitrogen atom. The term "halogen" refers to Cl, Br, F, or I.

The anti-progestin compounds of the present invention can be prepared as

25 described in the following schemes:

- 20 -

Scheme I



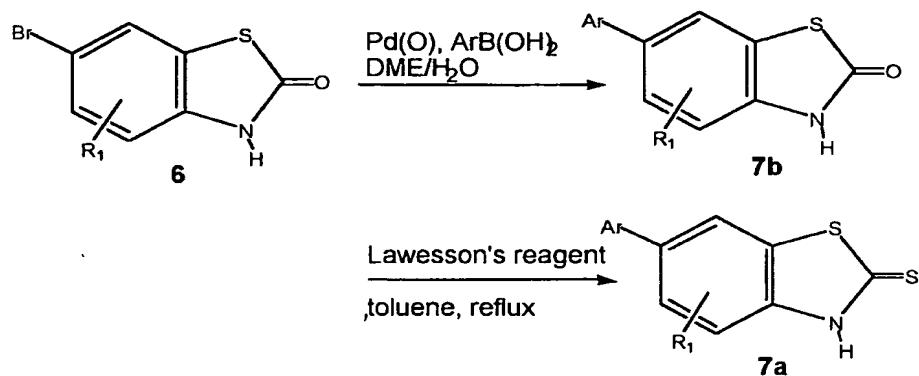
As illustrated in Scheme I, these compounds are generally prepared by employing the suitable coupling reaction as a final step and further converted to the thiourea analogues. Thus, an appropriately protected benzoimidazolinones 1 (Numerous protecting groups including but not limited to alkyloxycarbonyl such as BOC group can be employed in the starting material 1) readily prepared according to the procedure of Meanwell et al. (*J. Org. Chem.* **60**, 1565-1582(1995) can be alkylating at position-3 under a number of conditions. Among the reaction protocols, 5 compound 1 can be alkylated by treatment of 1 with a suitable base such as sodium hydride in an appropriate nonprotic solvent such as DMF followed by addition of an alkylating agent such as alkyl iodide or triflate. Alternatively, the compound 2 can be effected employing a Mitsunobu protocol. The conventional Mitsunobu reaction can 10

couple the compound **1** with an appropriate alcohol using a phosphorous reagent such as triphenyl phosphine and a dehydrating agent such as DEAD (diethyl azodicarboxylate) in a suitable solvent such as THF at the temperature ranging from 0 °C to the boiling point of the solvent which was employed. Deprotection of 5 compound **2** to give **3** can be furnished *via* numerous conditions such as acidic deprotection using an acid such as neat trifluoroacetic acid or basic deprotection employing a base such as sodium alkoxide in a suitable solvent such as THF or alcohol at temperature ranging from ambient temperature to the boiling point of the solvent employed. The compounds of this invention, **4**, can be readily prepared by employing 10 various coupling reactions including Suzuki, Stille protocols. These reactions are commonly performed in the presence of transition metallic catalyst, e.g., palladium or nickel complex often with phosphino ligands, e.g., Ph_3P , $1,1'$ -bis(diphenylphosphino)ferrocene, $1,2$ -bis(diphenylphosphino)ethane or a catalyst such as palladium acetate. Under this catalytic condition, an appropriately substituted 15 nucleophilic reagent, e.g., aryl boronic acid, arylstannane, or aryl zinc compound, is coupled with bromobenzoimidazolinones **3** to give compounds **4**. An appropriate base is often needed in the reaction, the commonly used bases include but not limited to sodium bicarbonate, sodium carbonate, potassium phosphate, barium carbonate, cesium fluoride, or potassium acetate. The most commonly used solvents in these 20 reactions include benzene, DMF, isopropanol, ethanol, DME, ether, acetone or a mixture of above solvent and water. The coupling reaction is generally executed under an inert atmosphere such as nitrogen or argon at temperatures ranging from room temperature to 95 °C.

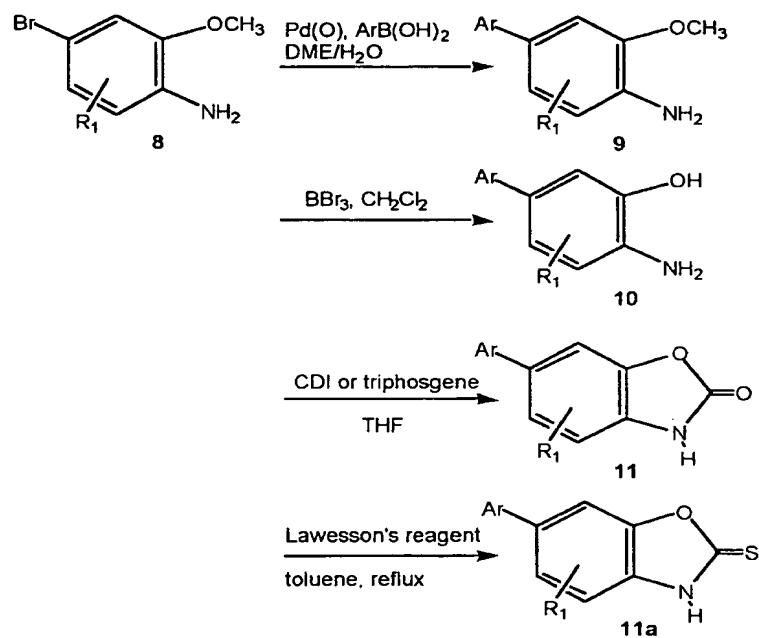
The anti-progestin compounds of this invention, **5**, can be easily prepared using 25 an appropriate sulfur reagent such as Lawesson's reagent or P_2S_5 in a suitable solvent such as toluene, xylene, chlorobenzene at reflux under an inert atmosphere such as nitrogen or argon.

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Scheme II



Scheme III



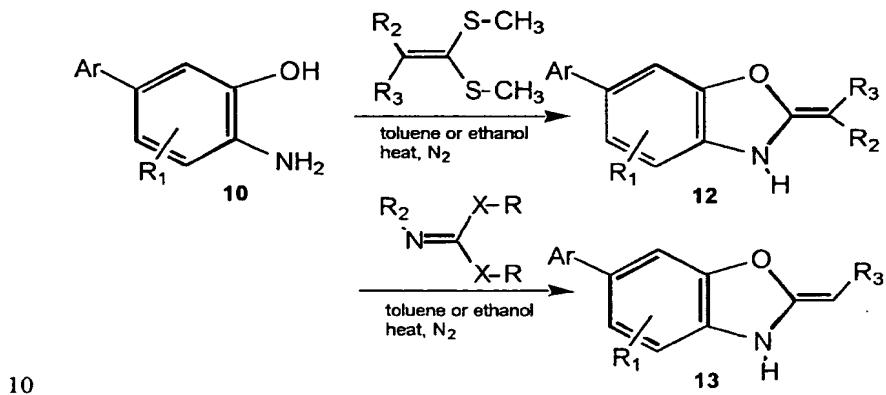
As shown in scheme II, 5-aryl benzothiazolinones 7 can be readily effected from an appropriate 5-bromo-benzothiazolinone 6 and a suitable electrophile such as aryl boronic acid, aryl tin reagent, or aryl zinc reagent *via* a suitable coupling reaction as described for the synthesis of benzimidazolinones 4. Conversion of 7 into 7a can be 5 effected using an appropriate sulfur reagent such as Lawesson's reagent or P₂S₅ in a suitable solvent such as toluene, xylene, chlorobenzene at reflux under an inert atmosphere such as nitrogen or argon.

The synthetic approaches leading to the 5-aryl benzoxazolinones 11 are described in scheme III. As illustrated in scheme III, an appropriately substituted 10 bromo *o*-anisidine can be coupled with an appropriate electrophile such as aryl boronic acid or aryl tin reagent *via* a coupling reaction as described for the synthesis of compounds 4 to give the biaryl 9. Demethylation of biaryl 9 to give amino phenol 10 can be furnished *via* various conditions including treatment of 9 with strong Lewis acid such as boron tribromide in a suitable solvent such as methylene chloride or treatment 15 of 9 with a mixture of a suitable Lewis acid such as aluminum chloride and a soft nucleophile such as thiol in a suitable solvent such as methylene chloride under an inert atmosphere such as argon or nitrogen. Ring closure of amino phenol 10 to produce the compounds of this invention 11 can be effected by using a appropriate condensing agent such as carbonyldiimidazole, phosgene, dimethylcarbonate, or diethylcarbonate 20 in a suitable nonprotic solvent such as THF at temperatures ranging from room temperature to 65 °C. Conversion of 11 into 11a can be accomplished using an appropriate sulfur reagent such as Lawesson's reagent or P₂S₅ in a suitable solvent such as toluene, xylene, chlorobenzene at reflux under an inert atmosphere such as nitrogen or argon.

25 Schemes IV, V, and VI describe the synthesis of other 5-aryl benzoimidazolinone, 5-aryl benzothiazolinone, 5-aryl benzoxazolinone bioisosteres. Using a similar procedure reported by Kondo et al. (Kondo, et al. *J. Med. Chem.* 33(7), 2012-2015(1990)) compound 12, 15, or 18 can be effected by treatment of compound 10, 14, or 17 with an appropriate ketene-*S, S*-acetals (at least one of R₂ or

R₃ is an electron withdrawing group.) in a suitable solvent such as toluene or anhydrous ethanol under an inert atmosphere such as nitrogen or argon at reflux. In a similar fashion, compound 13, 16, or 19 can be accomplished by reaction of compound 10, 14, or 17 with an appropriate imino-S, S-acetals or imino-acetals (R₂ is an electron withdrawing group.) employing a procedure similar to that of Evers, et al. (Evers, et al. *I. Prakt. Chem.* 333(5), 699-710 (1991)) or Haake et al. (Haake et al. *Synthesis-Stuttgart* 9, 753-758 (1991)) in a suitable solvent such as ethanol under an inert atmosphere such as argon or nitrogen at reflux.

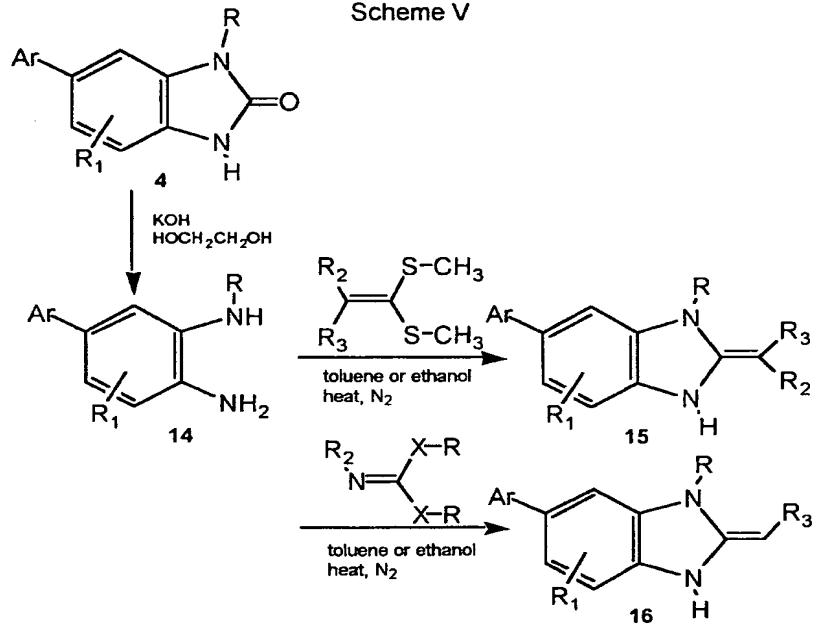
Scheme IV



Compounds 14 and 17 can be prepared as shown in schemes V and VI from compound 4 and 7 using a strong basic condition such as heating the compound in a mixture of potassium hydroxide and ethylene glycol at 165 °C under an inert atmosphere such as argon or nitrogen.

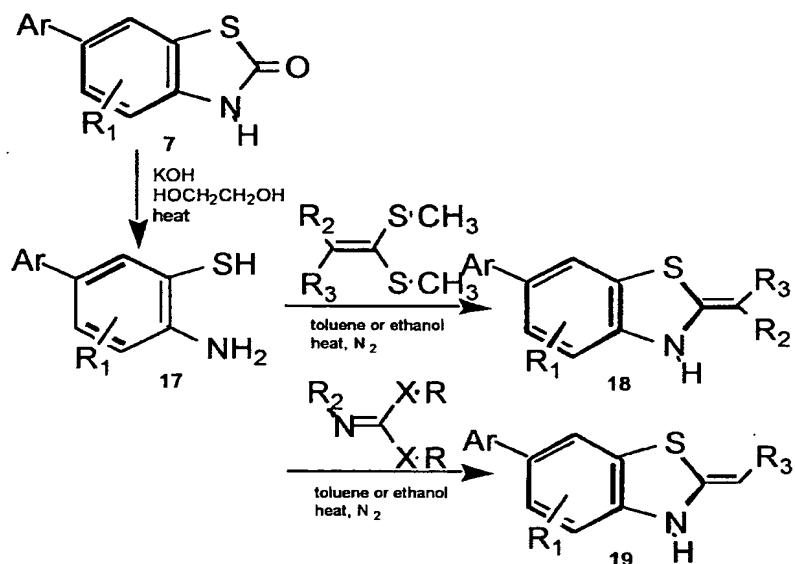
- 25 -

Scheme V



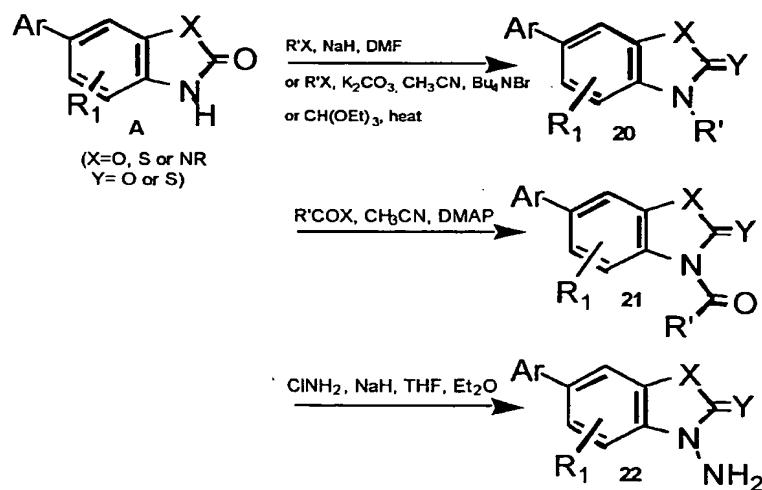
- 26 -

Scheme VI



As illustrated in Scheme VII, the compounds of this invention can be further derivatized at position-1 *via* numerous approaches leading to a variety of the novel 5 derivatives including 20, 21, and 22. Thus, alkyl or substituted alkyl derivatives 20 can be effected by treatment of compound A with a suitable base such as sodium hydride in suitable solvent such as DMF under an inert atmosphere such as argon or nitrogen followed by addition of an appropriate electrophile such as alkyl or substituted alkyl bromide, iodide, or triflate. Such transformation of A at position-1 can also be 10 effected using a biphasic condition as indicated in scheme VII in which alkylation is executed using a biphasic catalyst such as tributylammonium bromide in a suitable solvent such as acetonitrile. A further example of such modification includes, but is not limited to, the one depicted in Scheme VIII in that heating of A with triethyl orthoformate affords 1-substituted derivatives 20.

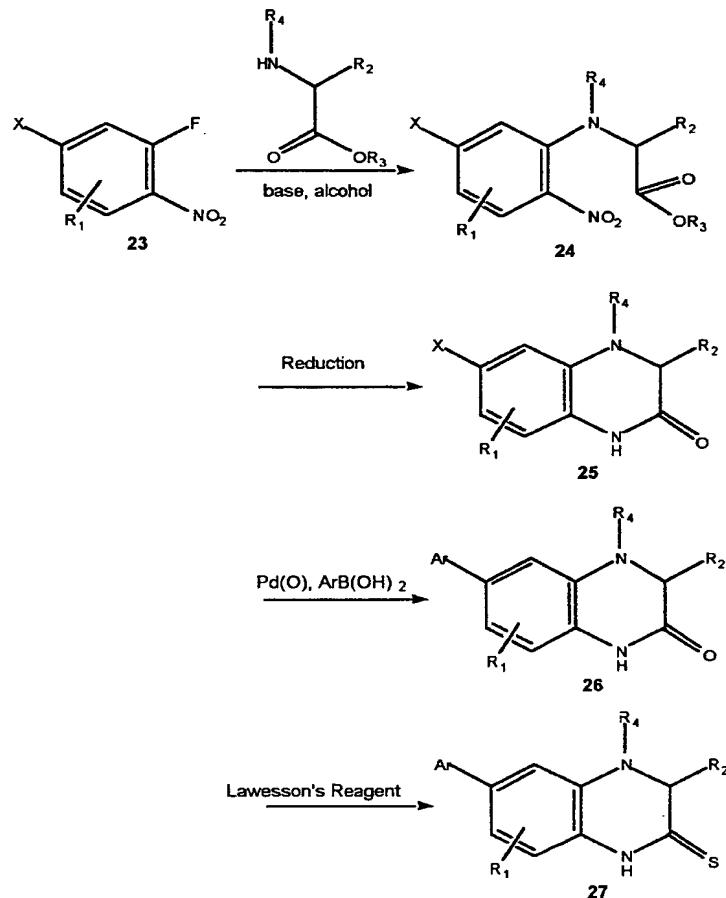
Scheme VII



The acylation or carboxylation of the compound A at position-1 to give compound 21 can be readily effected by treatment of A with a suitable acylating or carboxylating reagent such as di-*t*-butyl dicarbonate in the presence of a suitable basic catalyst such as DMAP in a suitable solvent such as acetonitrile under an inert atmosphere such as argon or nitrogen. The amination of position-1 of compound A to give compound 22 can be furnished using a suitable aminating reagent such as chloroamine in the presence of a suitable base such as sodium hydride in a suitable solvent such as THF or diethyl ether following the literature procedure (Metlesics et al. *J. Org. Chem.* **30**, 1311(1965)).

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Scheme XIII



Scheme VIII describes a procedure to prepare quinoxalin-4-ones. An appropriate *o*-fluoro nitro-benzene 23 (X = I, Br, Cl) is reacted with an appropriate substituted amino acid derivatives in the presence of a suitable base in a protic solvent such as alcohol to give compound 24 which is readily reduced by a suitable reducing agent such as tin chloride to furnish quinoxalin-2-one 25. The anti-progestational

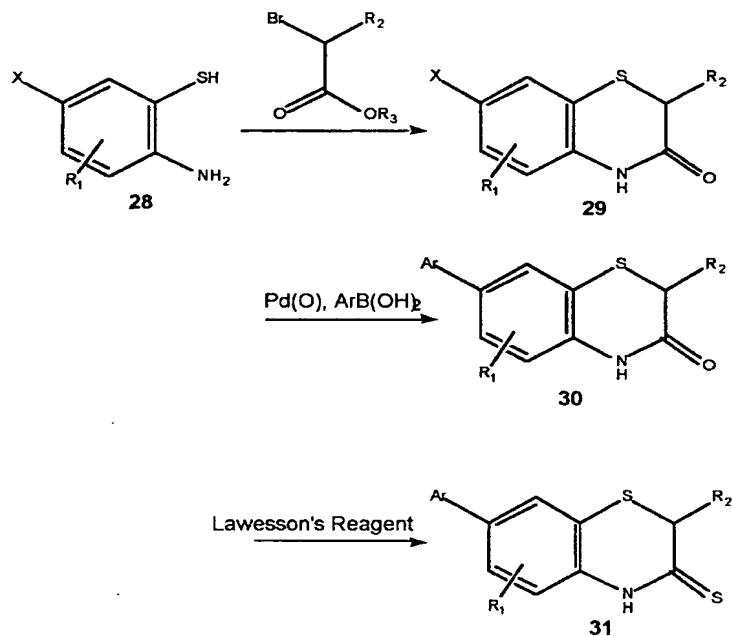
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- 29 -

compounds of this invention, **26**, can be easily effected by coupling an appropriate aryl boronic acid with compound **25** in a similar fashion as for the preparation of compound **9**. Conversion of **26** to **27** can be readily effected following the procedure of compound **11a**.

5

Scheme IX



Scheme IX illustrates an approach to prepare the benzothiazinones. Thus, an appropriately substituted *o*-amino benzenethiol **28** is treated with an appropriately substituted α -bromoacetate in a suitable solvent such as ethanol to afford compound **29** which can be readily coupled with an appropriate aryl boronic acid following the protocol of compound **9** to afford the compounds of this invention, **30**. Conversion of

10

30 to 31 can be carried out using a suitable sulfur reagent such as Lawesson's reagent according to procedure of compounds 11a.

The compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These 5 salts include, but are not limited to, the following salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium in the form of esters, carbamates and other 10 conventional "pro-drug" forms, which, when administered in such form, convert to the active moiety *in vivo*.

This invention includes pharmaceutical compositions comprising one or more compounds of this invention, preferably in combination with one or more pharmaceutically acceptable carriers and/or excipients. The invention also includes 15 methods of contraception and methods of treating or preventing maladies associated with the progesterone receptor, the methods comprising administering to a mammal in need thereof a pharmaceutically effective amount of one or more compounds as described above wherein Q is oxygen as antagonists of the progesterone receptor. The invention further provides comparable methods and compositions which utilize one or 20 more compounds herein wherein Q is S, NR⁶, or CR⁷R⁸ as agonists of the progesterone receptor.

The progesterone receptor antagonists of this invention, used alone or in combination, can be utilized in methods of contraception and the treatment and/or prevention of benign and malignant neoplastic disease. Specific uses of the 25 compounds and pharmaceutical compositions of invention include the treatment and/or prevention of uterine myometrial fibroids, endometriosis, benign prostatic hypertrophy; carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, meningioma and other hormone-dependent tumors. Additional uses of the

present progesterone receptor antagonists include the synchronization of the estrus in livestock.

When used in contraception the progesterone receptor antagonists of the current invention may be used either alone in a continuous administration of between 5 0.1 and 500 mg per day, or alternatively used in a different regimen which would entail 2-4 days of treatment with the progesterone receptor antagonist after 21 days of a progestin. In this regimen between 0.1 and 500 mg daily doses of the progestin (e.g. 10 levonorgestrel, trimegestone, gestodene, norethistrone acetate, norgestimate or cyproterone acetate) would be followed by between 0.1 and 500 mg daily doses of the progesterone receptor antagonists of the current invention.

The progesterone receptor antagonists of this invention, used alone or in combination, can also be utilized in methods of treatment and/or prevention of benign and malignant neoplastic disease. Specific uses of the compounds and pharmaceutical compositions of invention include the treatment and/or prevention of uterine 15 myometrial fibroids, endometriosis, benign prostatic hypertrophy; carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, meningioma and other hormone-dependent tumors. Additional uses of the present progesterone receptor antagonists include the synchronization of the estrus in livestock.

20 The progesterone receptor agonists of this invention, used alone or in combination, can be utilized in methods of contraception and the treatment and/or prevention of dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate. Additional uses of the invention include stimulation of food intake.

25 When used in contraception the progesterone receptor agonists of the current invention are preferably used in combination or sequentially with an estrogen agonist (e.g. ethinyl estradiol). The preferred dose of the progesterone receptor agonist is between 0.01 and 500 mg per day.

This invention also includes pharmaceutical compositions comprising one or more compounds described herein, preferably in combination with one or more pharmaceutically acceptable carriers or excipients. When the compounds are employed for the above utilities, they may be combined with one or more

5 pharmaceutically acceptable carriers or excipients, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or

10 parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

15 The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 500 mg/kg of animal body weight, preferably given in divided doses two to four

20 times a day, or in a sustained release form. For most large mammals, the total daily dosage is from about 1 to 100 mg, preferably from about 2 to 80 mg. Dosage forms suitable for internal use comprise from about 0.5 to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For

25 example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include

sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as 5 flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

10 These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary 15 conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

20 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringe ability exists. It must be stable under conditions of manufacture and storage and must be preserved against the 25 contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

The following non-limiting examples illustrate preparation and use of the compounds of the invention.

EXAMPLE 1

5-Bromo-2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid *tert*-butyl ester

Prepared via a literature procedure (*J. Org. Chem.* **60**(6), 1565-82 (1995)).

White solid: mp 148-149 °C; ¹H-NMR (DMSO-d₆) δ 11.4 (s, 1H), 7.6 (d, 1H, *J* = 8.57 Hz), 7.2 (dd, 1H, *J* = 8.57, 4.29 Hz), 7.1 (s, 1H), 1.6 (s, 9H); MS (ES) *m/z* 311([M-H]⁺, 70%), 313 ([M-H]⁺, 70%).

EXAMPLE 2

1-Benzyl-6-bromo-1,3-dihydro-benzoimidazol-2-one

10 A mixture of 5-bromo-2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid *tert*-butyl ester (2.5g, 8 mmol), benzyl bromide (1.2 mL, 10 mmol), potassium carbonate (1.38g, 10 mmol), and potassium iodide (50 mg) in the anhydrous acetonitrile was heated at 80 °C under nitrogen for 1 hour. The reaction mixture was cooled to room temperature and treated with a saturated aqueous ammonium chloride solution (30 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with brine (30 mL) and dried (MgSO₄). After removal of the solvent, the residue was taken up in trifluoroacetic acid (10 mL, neat) and the solution was stirred at room temperature under nitrogen for 10 minutes. The reaction solution was then treated with brine (30 mL) and ethyl acetate (50 mL). The organic layer was separated and dried (MgSO₄). After removal of the solvent, the residue was applied to a pad of silica gel to afford the title compound as white solid (1.89, 78%): mp 245-246 °C; ¹H-NMR (DMSO-d₆) δ 11.2 (s, 1H), 7.37-7.27 (m, 6H), 7.13 (dd, 1H, *J* = 8.25, 2.25 Hz), 6.95 (d, 1H, *J* = 8.25 Hz), 5.0 (s, 2H); MS (ES) *m/z* 301([M - H]⁺, 50%), 25 303([M - H]⁺, 50%).

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EXAMPLE 3

5-Bromo-3-methyl-2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid *tert*-butyl ester

A mixture of 5-bromo-2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid *tert*-butyl ester (4.0 g, 12.8 mmol), iodomethane (2.74 g, 9.2 mmol), and K₂CO₃ in CH₃CN (60 mL) was stirred at room temperature under a blanket of nitrogen overnight. Upon completion of the reaction, ethyl acetate (200 mL) was added and the organic layer was washed with H₂O (200 mL), dried over Na₂SO₄, and concentrated. The residue was purified *via* chromatography (silica gel, 25% ethyl acetate/hexane) to give 5-bromo-3-methyl-2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid *tert*-butyl ester as a white solid: mp 98-99 °C; ¹H-NMR (CDCl₃) δ 7.7 (d, 1H, J = 8.5 Hz), 7.27 (bs, 2H), 7.09 (d, 1H, J = 2 Hz), 3.4 (s, 3H), 1.7 (s, 9H); MS (ES) *m/z* 349([M + Na]⁺, 20%), 351([M + Na]⁺, 20%); Anal. Calc. For C₁₃H₁₅BrN₂O₃: C, 47.73, H, 4.62, N, 8.56. Found: C, 47.46, H, 4.5, N, 8.29.

15

EXAMPLE 4

6-Bromo-1-methyl-1,3-dihydro-benzoimidazol-2-one

Prepared from 5-bromo-3-methyl-2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid *tert*-butyl ester in the same fashion as that of Example 2. White solid: mp 237-238 °C; ¹H-NMR (DMSO-d₆) δ 11.0 (s, 1H), 7.35 (d, 1H, J = 1.58 Hz), 7.14 (dd, 1H, J = 7.89, 1.58 Hz), 6.92 (d, 1H, J = 7.89 Hz), 3.3 (s, 3H); MS (ES) *m/z* 227([M + H]⁺, 50%), 229([M + H]⁺, 50%); Anal. Calc. For C₈H₇BrN₂O: C, 42.32, H, 3.11, N, 12.34. Found: C, 42.35, H, 3.07 N, 11.89.

25

EXAMPLE 5

1-Benzyl-6-(3-chloro-phenyl)-1,3-dihydro-benzoimidazol-2-one

A mixture of 1-benzyl-6-bromo-1,3-dihydro-benzoimidazol-2-one (0.75 g, 2.5 mmol), 3-chloro-phenyl boronic acid (0.4 g, 2.6 mmol), tetrakis(triphenylphosphine)-palladium (0) (0.23 g, 0.2 mmol), and potassium carbonate (0.72 g, 5.2 mmol) in

toluene (15 mL) and H₂O (8 mL) was subject to a blanket of nitrogen for 15 minutes at 50 °C and then heated to 85 °C for 1 hour. The reaction mixture was cooled to room temperature and ethyl acetate (100 mL) was added. The organic layer was washed twice with aqueous ammonium chloride (30 mL) and once with brine (30 mL), 5 dried over magnesium sulfate and concentrated. After removal of the solvent, the residue was purified *via* chromatography (silica gel, 25% ethyl acetate/hexane) to give 1-benzyl-6-(3-chloro-phenyl)-1,3-dihydro-benzoimidazol-2-one as a white solid (0.134 g, 16%): mp 168-169 °C; ¹H-NMR (DMSO-d₆) δ 11.0 (s, 1H), 7.66 (t, 1H, *J* = 2.05 Hz), 7.58-7.5 (m, 1H), 7.45 (t, 2H, *J* = 8.18 Hz), 7.37-7.22 (m, 7 H), 7.08 (d, 1H, *J* = 10 8.18 Hz), 5.1 (s, 2H); MS (ES) *m/z* 333([M - H]⁺, 100%); Anal. Calc. For C₂₀H₁₅ClN₂O: C, 71.75, H, 4.52, N, 8.37. Found: C, 70.27, H, 4.56, N, 8.0.

EXAMPLE 6

1-Benzyl-6-(3-nitro-phenyl)-1,3-dihydro-benzoimidazol-2-one

15 Prepared from 1-benzyl-6-bromo-1,3-dihydro-benzoimidazol-2-one and 3-nitro-phenyl boronic acid in the same fashion as that of Example 5. White solid: mp 202-203 °C; ¹H-NMR (DMSO-d₆) δ 11.2 (s, 1H), 8.38 (t, 1H, *J* = 1.97 Hz), 8.15 (dd, 1H, *J* = 7.83, 1.97 Hz), 8.80 (d, 1H, *J* = 7.83 Hz), 7.72 (t, 1H, *J* = 7.83 Hz), 7.56 (bs, 1H), 7.43-7.22 (m, 6H), 7.13 (d, 1H, *J* = 7.83 Hz), 5.1 (s, 2H); MS (ES) *m/z* 344([M - H]⁺, 100%); Anal. Calc. For C₂₀H₁₅N₃O₃ 0.25 H₂O: C, 68.66, H, 4.46, N, 12.01. Found: C, 68.42, H, 4.44, N, 11.77.

EXAMPLE 7

1-Methyl-6-(3-nitro-phenyl)-1,3-dihydro-benzoimidazol-2-one

25 Prepared from 1-methyl-6-bromo-1,3-dihydro-benzoimidazol-2-one and 3-nitro-phenyl boronic acid in the same fashion as that of Example 5. White solid: mp 264-265 °C; ¹H-NMR (DMSO-d₆) δ 11.0 (s, 1H), 8.47 (t, 1H, *J* = 1.5 Hz), 8.19-8.15 (m, 2H), 7.75 (t, 1H, *J* = 8.25 Hz), 7.58 (d, 1H, *J* = 1.5 Hz), 7.43 (dd, 1H, *J* = 8.25, 1.5 Hz), 7.1 (d, 1H, *J* = 8.25 Hz), 3.37 (s, 3H); MS (ES) *m/z* 268([M - H]⁺, 50%);

Anal. Calc. For $C_{14}H_{11}N_3O_3$: C, 62.45, H, 4.12, N, 15.61. Found: C, 61.48, H, 4.36 N, 14.75.

EXAMPLE 8

5 **6-(3-chloro-phenyl)-1-methyl-1,3-dihydro-benzoimidazol-2-one**

Prepared from 1-methyl-6-bromo-1,3-dihydro-benzoimidazol-2-one and 3-chloro-phenyl boronic acid in the same fashion as that of Example 5. mp 219-220 °C; 1H -NMR (DMSO- d_6) δ 11.0 (s, 1H), 7.75 (bs, 1H), 7.65 (dd, 1H, J = 7.5, 1.76 Hz), 7.49-7.44 (m, 2H), 7.39-7.32 (m, 2H), 7.06 (d, 1H, J = 7.94 Hz), 3.35 (s, 3H); MS 10 (ES) m/z 259([M + H] $^+$, 100%); Anal. Calc. For $C_{14}H_{11}ClN_2O$: C, 65, H, 4.29, N, 10.83. Found: C, 64.44, H, 4.36 N, 10.6.

EXAMPLE 9

5 **5-(3-Nitro-phenyl)-1,3-dihydro-benzoimidazol-2-one**

15 Prepared from 5-bromo-1,3-dihydro-benzoimidazol-2-one and 3-nitro-phenyl boronic acid in the same fashion as that of Example 5. White solid: mp 324-325 °C; 1H -NMR (DMSO- d_6) δ 10.8 (s, 2H), 8.4 (m, 1H), 8.15 (d, 1H, J = 7.5 Hz), 8.1 (d, 1H, J = 7.5 Hz), 7.7 (t, 1H, J = 7.5 Hz), 7.35 (d, 1H, J = 7.5 Hz), 7.3 (s, 1H), 7.05 (d, 1H, J = 7.5 Hz); MS (ES) m/z 254 ([M - H] $^+$, 100%); Anal. Calc. For $C_{13}H_9N_3O_3$: C, 61.18, H, 3.55, N, 16.46. Found: C, 60.5, H, 3.69 N, 15.53.

EXAMPLE 10

4 **Amino-3'-nitro-biphenyl-3-ol**

4-Amino-3-methoxy-3'-nitro-biphenyl was prepared from 4-bromo-2-methoxyaniline (*Synth. Commun.* 23(6), 855-9(1993)) and 3-nitrophenyl boronic acid according to the procedure of Example 5. White solid: mp 167-168 °C; 1H -NMR ($CDCl_3$) δ 8.39 (t, 1H, J = 1.97 Hz), 8.13-8.09 (m, 1H), 7.88-7.84 (m, 1H), 7.55 (t, 1H, J = 8.0 Hz), 7.09 (dd, 1H, J = 7.98, 1.94 Hz), 7.04 (d, 1H, J = 1.89 Hz), 6.80 (d, 1H, J = 8.04 Hz), 4.0 (s, 5H).

4-Amino-3-methoxy-3'-nitro-biphenyl was then stirred with boron tribromide in dichloromethane to give 4-amino-3'-nitro-biphenyl-3-ol as an orange solid: mp 175-176 °C; ¹H-NMR (DMSO-d₆) δ 9.3 (s, 1H), 8.25 (bs, 1H), 8.05 (d, 1H, *J* = 8.33 Hz), 7.95 (d, 1H, *J* = 8.33 Hz), 7.66 (t, 1H, *J* = 7.5 Hz), 7.06-7.02 (m, 2H), 6.70 (d, 5 1H, *J* = 8.33 Hz), 4.9 (s, 2H); MS (ES) *m/z* 229 ([M - H]⁺, 100%).

EXAMPLE 11

6-(3-Nitro-phenyl)-3H-benzooxazol-2-one

A solution of 4-amino-3'-nitro-biphenyl-3-ol (0.115 g, 0.5 mmol) in dry THF 10 (2.5 mL) was treated with a solution of 1,1'-carbonyldiimidazole (0.098 g, 0.6 mmol) in dry THF (2.5 mL). The reaction mixture was stirred at room temperature under a blanket of nitrogen for 6 hours. A precipitate formed, was collected and washed with methylene chloride (50 mL) to give 6-(3-nitro-phenyl)-3H-benzooxazol-2-one (0.095 g, 74%) as a white solid: mp 280-281 °C; ¹H-NMR (DMSO-d₆) δ 11.7 (s, 1H), 8.43 (t, 1H, *J* = 1.15 Hz), 8.2-8.13 (m, 2H), 7.79-7.72 (m, 2H), 7.59 (dd, 1H, *J* = 8.08, 15 2.31 Hz), 7.21 (d, 1H, *J* = 8.08 Hz), MS (ES) *m/z* 255([M - H]⁺, 100%); Anal. Calc. For C₁₃H₈N₂O₄: C, 60.94, H, 3.15, N, 10.93. Found: C, 59.95, H, 3.17 N, 10.77.

EXAMPLE 12

6-(3-Nitro-phenyl)-3H-benzothiazol-2-one

A mixture of 6-bromo-2-benzothiazolinone (5.0 g, 21.7 mmol), 3-nitrophenyl 20 boronic acid (5.0 g, 30.0 mmol), tetrakis(triphenylphosphine)-palladium (0) (1.73 g, 1.5 mmol), and potassium carbonate (8.0 g, 58.0 mmol) in toluene (100 mL), H₂O (20 mL), and ethanol (30 mL) was subject to a blanket of nitrogen for 15 minutes at 50 °C 25 and then was heated at 85 °C for 24 hours. The reaction mixture was cooled to room temperature and ethyl acetate (100 mL) was added. The organic layer was washed with aqueous ammonium chloride (2x50 mL) and with brine (100 mL), dried over magnesium sulfate and concentrated. The residue was purified via chromatography (silica gel, 25% ethyl acetate/hexane) to give 6-(3-nitro-phenyl)-3H-benzothiazol-2-

one as a brown solid (0.1 g, 1.8 %): mp 276-277 °C; ¹H-NMR (DMSO-d₆) δ 11 (s, 1H), 8.44 (t, 1H, *J* = 2.7 Hz), 8.21-8.08 (m, 3H), 7.78-7.69 (m, 2H), 7.24 (d, 1H, *J* = 9.23 Hz); MS (ES) *m/z* 271 ([M - H]⁻, 100%); Anal. Calc. For C₁₃H₈N₂O₃S 0.25 H₂O: C, 56.41, H, 3.10, N, 10.12. Found: C, 56.48, H, 3.11, N, 9.99.

5

EXAMPLE 13**6-(3-Chloro-phenyl)-3H-benzothiazol-2-one**

Prepared from 6-bromo-2-benzothiazolinone, 3-nitrophenyl boronic acid according to the procedure of example 12. A white solid: mp 195-196 °C; ¹H-NMR (DMSO-d₆) δ 11.95 (s, 1H), 7.96 (d, 1H, *J* = 1.17 Hz), 7.7 (t, 1H, *J* = 1.76 Hz), 7.62-7.59 (m, 2H), 7.46 (t, 1H, *J* = 7.65 Hz), 7.4-7.38 (m, 1H), 7.18 (d, 1H, *J* = 8.24 Hz); MS (EI) *m/z* 261 (M⁺, 30%); Anal. Calc. For C₁₃H₈ClNO₃ 0.5 H₂O: C, 57.67, H, 3.35, N, 5.17. Found: C, 57.98, H, 3.11, N, 4.98.

15

EXAMPLE 14**7-(3-Nitro-phenyl)-4H-benzo[1,4]thiazin-3-one**

A mixture of 2-amino-5-bromo-benzenethiol (20 g, 0.1 mol), ethyl bromoacetate (19 g, 0.1 mol), and sodium bicarbonate (8.8 g, 0.1 mol) in DMF (200 ml) was heated to reflux for 2 hours. The mixture was diluted with water and extracted with ethyl acetate (2x100 mL). The combined organic extracts were washed with water, then brine, dried (MgSO₄) and evaporated to obtain the crude 7-bromo-4H-benzo[1,4]thiazin-3-one (20 g, 82%). A small portion of sample was recrystallized from ethanol to afford pure 7-bromo-4H-benzo[1,4]thiazin-3-one: mp 212-213 °C; MS (EI) *m/z* 243/245 (M⁺).

25 A solution of 7-bromo-4H-benzo[1,4]thiazin-3-one (2 g, 8.2 mmol), 3-nitrophenyl boronic acid (2.72 g, 16.4 mmol), potassium carbonate (6.85 g, 49.2 mmol), and tetrakis(triphenylphosphine) palladium(0) (0.95 g, 0.82 mmol) in dimethoxyethane (100 ml), ethanol (25 ml), and water (25 ml) was heated to reflux for

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6 hours. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc (3x50 mL). The combined organic extracts were washed with water, then brine, dried (MgSO_4) and evaporated to obtain crude 7-(3-nitro-phenyl)-4H-benzo[1,4]thiazin-3-one (0.15 g, 6%). Recrystallization of crude sample from 5 EtOAc afforded the title compound: mp 290–292 °C; MS (EI) m/z 286 (M^+).

EXAMPLE 15

2-Ethyl-7-(3-nitro-phenyl)-4H-benzo[1,4]thiazin-3-one

To a mixture of 2-amino-5-bromo-benzenethiol (20 g, 0.1 mol) and cesium 10 carbonate (33 g, 0.1 mol) in DMF (500 ml) at –35 °C was added dropwise 2-bromobutyrylbromide (23 g, 0.1 mol). The mixture was allowed to warm to room temperature, poured into ice/water, and extracted with CH_2Cl_2 (2x50 mL). The combined organic extracts were washed with water, then brine, dried (MgSO_4) and evaporated. The residue was purified by column chromatography (SiO_2 , ethyl 15 acetate:hexane/1:6) to afford 7-bromo-2-ethyl-4H-benzo[1,4]thiazin-3-one (3.7 g, 14%): mp 100 °C; MS (EI) m/z 271/273 (M^+).

A solution of 7-bromo-2-ethyl-4H-benzo[1,4]thiazin-3-one (2 g, 7.3 mmol), 3-nitrophenyl boronic acid (1.22 g, 7.3 mmol), potassium carbonate (3 g, 22 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.84 g, 0.72 mmol) in dimethoxyethane (100 20 ml), ethanol (25 ml), and water (25 ml) was heated to reflux for 6 hours. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc (3x40 mL). The combined organic extracts were washed with water, then brine, dried (MgSO_4) and evaporated. The residue was recrystallized from ethanol to afford the title compound as tan crystals (0.17 g, 7.3%): mp 180 °C; MS (EI) m/z 314 (M^+).

EXAMPLE 16

8-(3-Chloro-phenyl-1,2,3,3a-tetrahydro-5H-pyrrolo[1,2-
alquinolin-4-one

To a mixture of acetic acid (500 ml), 30% hydrogen peroxide (250 ml), and 5 concentrated sulfuric acid (10 ml) was added 4-bromo-2-fluoroaniline (50 g, 0.26 mol) at 85 ± 5 °C over 20 minutes. The reaction mixture was allowed to cool to room temperature and filtered. The solution was diluted with water and extracted with EtOAc (2x100 mL). The combined organic extracts were washed with water, then brine, dried (MgSO_4) and evaporated. The semisolid residue was filtered and the 10 crude 4-bromo-2-fluoro-1-nitro-benzene was sublimed *in vacuo* to afford 4-bromo-2-fluoro-1-nitro-benzene (23 g, 40%): mp 82–83 °C; $^1\text{H-NMR}$ (DMSO-d_6) δ 7.64 – 7.70 (m, 1H), 8.0 (dd, 1H, $J = 11.0, 1.98$ Hz), 8.1 (t, 1H, $J = 8.57$ Hz); MS (EI) m/z 219/221 (M^+).

A mixture of 4-bromo-2-fluoro-1-nitro-benzene (9 g, 40 mmol), L-proline 15 (4.6g, 40 mmol), and potassium carbonate (7 g, 50 mmol) in ethanol (50 ml) and water (40 ml) was heated to reflux for 5 hours. After cooling to room temperature, the mixture was diluted with water and was adjusted to pH 6 with 1N aqueous HCl solution. The mixture was extracted with EtOAc (2x100 mL), the combined organic extracts were washed with water, then brine, dried (MgSO_4) and evaporated to afford 20 *N*-(5-bromo-2-nitro-phenyl)-pyrrolidine-2-carboxylic acid (6 g, 48%) which was used in next step without further purification.

A solution of *N*-(5-bromo-2-nitro-phenyl)-pyrrolidine-2-carboxylic acid (6g, 23 mmol) and tin(II) chloride dihydrate (16.5 g, 73 mmol) in ethanol (200 ml), water (30 ml) and concentrated HCl (10 ml) was heated to reflux for 6 hours. After cooled to 25 room temperature, the mixture was diluted with water and was adjusted to pH 9 with 2N aqueous sodium hydroxide solution. After addition of EtOAc, the precipitated tin hydroxide was filtered off. The layers were separated and the organic layer was washed with water, then brine, dried (MgSO_4) and evaporated to afford 8-bromo-

1,2,3,3a-tetrahydro-5H-pyrrolo[1,2-a]quinoxalin-4-one (3.7 g, 60%), which was used without further purification.

A solution of 8-bromo-1,2,3,3a-tetrahydro-5H-pyrrolo[1,2-a]quinoxalin-4-one (2.7 g, 10 mmol), 3-chlorophenyl boronic acid (1.6 g, 10 mmol), potassium carbonate (4 g, 30 mmol), and tetrakis(triphenylphosphine) palladium(0) (0.5 g, 0.43 mmol) in dimethoxyethane (100 ml), ethanol (25 ml), and water (25 ml) was heated to reflux for 6 hours. After cooled to room temperature, the mixture was diluted with water and extracted with EtOAc (3x60 mL). The combined organic extracts were washed with water, then brine, dried (MgSO_4) and evaporated. The crude product (1.5 g) was 10 recrystallized from EtOAc/hexane to afford the title compound (0.2 g, 7%): mp 210°C; MS (+APCI) m/z 299 ($[\text{M}+\text{H}]^+$).

EXAMPLE 17

6-(3-Chloro-phenyl)-4-methyl-3,4-dihydro-1H-quinoxalin-4-one

15 (5-Bromo-2-nitro-phenyl)-methyl-amino]-acetic acid.

A mixture of 4-bromo-2-fluoro-1-nitro-benzene (9 g, 40 mmol), sarcosine (3.6g, 40 mmol), and potassium carbonate (5.5 g, 40 mmol) in ethanol (100 ml) and water (40 ml) was heated to reflux for 5 hours. After cooling to room temperature, the mixture was diluted with water and was adjusted to pH 6 with 1N aqueous HCl 20 solution. The yellow precipitate was collected, washed with water and dried *in vacuo* to obtain crude [(5-bromo-2-nitro-phenyl)-methyl-amino]-acetic acid (10 g, 87%). A portion of the crude sample was recrystallized from EtOAc/hexane to afford the pure [(5-bromo-2-nitro-phenyl)-methyl-amino]-acetic acid: mp 152–155 °C; $^1\text{H-NMR}$ (DMSO- d_6) δ 2.81 (s, 3H), 4.00 (s, 2H), 7.06 (dd, 1H, J = 8.79, 1.98 Hz), 7.22 (d, 1H, J = 1.98 Hz), 7.69 (d, 1H, J = 8.79 Hz), 12.8 (s, 1H); MS (+APCI) m/z 289/291 25 ($\text{M}+\text{H}]^+$).

A solution of [(5-bromo-2-nitro-phenyl)-methyl-amino]-acetic acid (8g, 27.6 mmol) and tin(II) chloride dihydrate (20 g, 88 mmol) in ethanol (200 ml), water (30 ml) and concentrated HCl (10 ml) was heated to reflux for 6 hours. After cooling to room temperature the mixture was diluted with water and was adjusted to pH 9 with 5 2N aqueous sodium hydroxide solution. After addition of EtOAc, the precipitated tin hydroxide was filtered off. The layers were separated and the organic layer was washed with water, then brine, dried (MgSO_4) and evaporated. The residue was recrystallized from ethanol to afford 6-bromo-4-methyl-3,4-dihydro-1H-quinoxalin-2-one (2.4 g, 36%), which was used without further purification. $^1\text{H-NMR}$ (DMSO-d_6) 10 δ 2.78 (s, 3H), 3.89 (s, 2H), 6.81 (d, 1H, J = 1.76 Hz), 6.95 (dd, 1H, J = 8.49, 1.81 Hz), 7.05 (d, 1H, J = 8.47 Hz), 10.63 (s, 1H).

A solution of 6-bromo-4-methyl-3,4-dihydro-1H-quinoxalin-2-one (2.4 g, 10 mmol), 3-chlorophenyl boronic acid (1.6 g, 10 mmol), potassium carbonate (4 g, 30 mmol), and tetrakis(triphenylphosphine) palladium(0) (0.5 g, 0.43 mmol) in 15 dimethoxyethane (100 ml), ethanol (25 ml), and water (25 ml) was heated to reflux for 6 hours. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc (3x50 mL). The combined organic extracts were washed with water, then brine, dried (MgSO_4) and evaporated. The residue was purified by column chromatography (SiO_2 , EtOAc:hexane/1:6) to afford the title compound (0.58 g, 20 21%): mp 140 °C; $^1\text{H-NMR}$ (DMSO-d_6) δ 2.82 (s, 3H), 3.65 (s, 2H), 6.82 (d, 1H, J = 7.91 Hz), 6.90 (d, 1H, J = 1.76 Hz), 6.99 (dd, 1H, J = 8.13, 1.98 Hz), 7.3–7.32 (m, 1H), 7.39 (t, 1H, J = 7.91 Hz), 7.55 (dt, 1H, J = 7.91, 1.10 Hz), 7.64 (t, 1H, J = 1.98 Hz), 10.47 (s, 1H); MS ((+)APCI) m/z 299 (M+H^+).

EXAMPLE 18

25 5-(3, 4-Dihydro-4-methyl-2-oxo-quinaxalin-6-yl) thiophene-3-carbonitrile
3,4-Dihydro-4-methyl-2-oxo-quinoxalin-6-yl) boronic acid.

To a solution of 6-bromo-4-methyl-3,4-dihydro-1H-quinoxalin-2-one (3.6g, 15 mmol) in THF (100ml) was added sodium hydride (0.6g, 15 mmol, 60% dispersion in

mineral oil). After stirring 30 min. at room temperature, the mixture was cooled to - 78°C and butyl lithium (2.5M in hexanes, 6 ml, 15 mmol) was added slowly. After 30 min. triisopropyl borate (7ml, 30 mmol) was added and the mixture was allowed to warm to room temperature. After 2 hrs. hydrochloric acid (1N, 200 ml) and EtOAc (200 ml) were added. After stirring for 30 min., the pH was adjusted to 6 and the layers were separated. The aqueous phase was extracted with EtOAc, then the combined organic layers were washed with water, brine, dried (MgSO_4) and evaporated. The residue was triturated with ether, the precipitate was filtered off and dried in vacuo to obtain the subtitled compound (1.6g, 52%) as an off-white solid: $^1\text{H-NMR}$ (DMSO- d_6) δ 2.78 (s, 3H), 3.62 (s, 2H), 6.75 (d, J = 7.58Hz, 1H), 7.16 (s, 1H), 7.18 (d, J = 7.86 Hz, 1H), 7.85 (s, 2H), 10.45 (s, 1H). MS (EI) m/z 207 ($\text{M}+\text{H}$)⁺.

A mixture of 3,4-dihydro-4-methyl-2-oxo-quinoxalin-6-yl) boronic acid (1.6g, 80 mmol), 2-bromo-4-cyanothiophene (1.5 g, 80 mmol), potassium carbonate (3.3g, 24 mmol) and tetrakis(triphenylphosphine) palladium (0) (0.25g, 0.2 mmol) in dimethoxyethane (70 ml), ethanol (15 ml), and water (15 ml) was heated to reflux for 6 hrs. After cooling to room temperature the mixture was diluted with water and extracted with EtOAc (3x40 mL). The combined organic layers were washed with water, then brine, dried (MgSO_4) and evaporated to obtain crude product (0.85g, 40%). The residue was purified by column chromatography (SiO_2 , 40% acetonitrile, 60% water) to afford the title compound: mp 270 °C; $^1\text{H-NMR}$ (DMSO- d_6) δ 2.84 (s, 3H), 3.70 (s, 2H), 6.82 (d, J = 7.91 Hz, 1H), 6.96 (d, J = 1.76 Hz, 1H), 7.02 (dd, J = 7.91, 1.76 Hz, 1H), 7.83 (d, J = 1.32 Hz, 1H) 8.44 (d, J = 1.32 Hz, 1H), 10.56 (s, 1H); MS (EI) m/z 269 (M^+).

25

EXAMPLE 19

4-(n-Butyl)-6-(3-chloro-phenyl)-3,4-dihydro-1H quinoxalin-2-one

[(5-Bromo-2-nitro-phenyl)-n-butyl-amino]acetic acid

A mixture of 4-bromo-2-fluoro-nitro benzene (34 g, 0.15 mol), N-n-butyl glycine (20 g, 0.15 mol) in ethanol (600 ml), and water (150 ml) was heated to reflux

for 6 hours. After cooling to room temperature, the mixture was diluted with 2N sodium hydroxide, extracted with CH_2Cl_2 and pH was adjusted to 5 with 1N HCl. The mixture was extracted with CH_2Cl_2 , the CH_2Cl_2 solution was dried (MgSO_4) and evaporated to obtain the crude product (11 g, 22%) as a brown oil, which was used 5 without further purification. $^1\text{H-NMR}$ (DMSO-d_6) δ 0.84 (t, J = 7.30 Hz, 3H), 1.23 (m, 2H), 1.45 (m, 2H), 3.18 (t, J = 7.30 Hz, 2H), 3.91 (s, 2H), 7.16 (dd, J = 8.68, 1.91 Hz, 1H), 7.40 (d, J = 1.94 Hz, 1H), 7.69 (d, J = 8.68 Hz, 1H); MS (EI) m/z 331 (M^+).

6-Bromo-4-(n-butyl)-3,4-dihydro-1H-quinoxalin-2-one.

10 To a solution of [(5-bromo-2-nitro-phenyl)-n-butyl-amino]acetic acid (11g, 33 mmol) in acetic acid (150 ml) was added iron powder (6g, 107 mmol) and the mixture was stirred for 2 hrs at 90°C. The reaction mixture was cooled and filtered and the acetic acid was evaporated. The remaining slurry was extracted with CH_2Cl_2 (3x50 mL). The combined CH_2Cl_2 extracts were combined, dried (MgSO_4) and evaporated 15 (8.5 g, 90%). The product was used without further purification. $^1\text{H-NMR}$ (DMSO-d_6) δ 0.93 (t, J = 6.81 Hz, 3H), 1.35 (m, 2H), 1.51 (m, 2H), 3.18 (t, J = 6.92 Hz, 2H), 3.75 (s, 2H), 6.6-6.9 (m, 3H), 10.50 (s, 1H).

20 A solution of 6-bromo-4-(n-butyl)-3,4-dihydro-1H-quinoxalin-2-one (8.5g, 30 mmol), 3-chlorophenyl boronic acid (5g, 30 mmol), potassium carbonate (12.5g, 90 mmol) and tetrakis- (triphenylphosphine) palladium (0) (1.3g, 1.1 mmol) in 25 dimethoxyethane (200 ml), ethanol (50 ml), and water (50 ml) was heated to reflux for 6 hrs. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc (3x). The combined organic layers were washed with water, then brine, dried (MgSO_4) and evaporated to obtain crude product (7g, 74%). The residue was purified by column chromatography (SiO_2 , 20% EtOAc, 80% hexane) to afford the title compound, mp 110-115°C. $^1\text{H-NMR}$ (DMSO-d_6) δ 0.93 (t, J = 7.35 Hz, 3H), 1.36 (m, 2H), 1.56 (m, 2H), 3.30 (m, 2H), 3.74 (s, 2H), 6.84 (d, J = 8.13 Hz, 1H), 6.90 (d, J = 1.54 Hz, 1H), 6.95 (dd, J = 8.13, 1.54 Hz, 1H) 7.35 (m, 1H), 7.43

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(t, $J = 7.91$ Hz, 1H), 7.55 (m, 1H), 7.63 (t, 1.76 Hz, 1H), 10.50 (s, 1Hz). MS (I+) APC I) m/z 315 [M+H]⁺ + 1 chlorine.

EXAMPLE 20

5

6-(3-Cyano-5-fluorophenyl)-4-isopropyl-3,4-dihydro-1H- quinoxalin-2-one

[(5-Bromo-2-nitro-phenyl)-isopropyl-amino]-acetic acid.

A mixture of 4-bromo-2-fluoro-1-nitrobenzene (52 g, 0.24 mol), n-isopropylglycine (26 g, 0.22 mol), potassium carbonate (32 g, 0.23 mol) in ethanol 10 (700 ml) and water (140 ml) was heated to reflux for 3 hrs. After cooling to room temperature the mixture was diluted with water, extracted with CHCl₃, and the pH was adjusted to 5 with 1N HCl. The yellow precipitate was filtered off, washed with water and dried in vacuo (31 g, 44%): ¹H-NMR (DMSO-d₆) δ 1.08 (d, $J = 6.50$ Hz, 6H), 3.55 (septet, $J = 6.50$ Hz, 1H), 3.92 (s, 2H), 7.25 (dd, $J = 8.65, 1.72$ Hz, 1H), 15 7.53 (d, $J = 1.69$ Hz, 1H), 7.69 (d, $J = 8.65$ Hz, 1H), 12.52 (bs, 1H).

6-Bromo-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one.

To a solution of [(5-bromo-2-nitro-phenyl)-isopropyl-amino] acetic acid (27 g, 85 mmol) in acetic acid (400 ml) was added iron powder (15 g, 0.27 mol) and the mixture was stirred for 2 hrs. at 90 °C. The reaction mixture was cooled, filtered, and 20 the acetic acid was evaporated. The remaining slurry was extracted with CH₂Cl₂ (3 x 300 ml). The CH₂Cl₂ extracts were combined, dried (MgSO₄) and evaporated to afford the subtitled compound (16.8 g, 73%): ¹H-NMR (DMSO-d₆) δ 1.13 (d, $J = 6.54$ Hz, 6H), 3.57 (s, 2H), 3.99 (septet, $J = 6.54$ Hz, 1H), 6.82 (dd, $J = 8.23, 1.88$ Hz, 1H), 6.72 (d, $J = 8.17$ Hz, 1H), 6.90 (d, $J = 1.59$ Hz, 1H), 10.50 (s, 1H): MS (EI) 25 267/269 (M)⁺ + 1 bromine.

(4-Isopropyl-2-oxo-3,4-dihydro-quinoxalin-6-yl)boronic acid.

To a solution of 6-bromo-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one (8.1 g, 30 mmol) in THF (200 ml) was added sodium hydride (60% dispersion in mineral oil, 1.2 g, 30 mmol). After stirring for 30 min. at room temperature, the mixture was

cooled to -78 °C and butyl lithium (2.5 M in hexanes, 12.5 ml, 30 mmol) was added slowly. After 30 min. triisopropyl borate (19 ml, 83 mmol) was added and the mixture was allowed to warm to room temperature. After 2 hours, hydrochloric acid (1N, 350 ml) and ethyl acetate (350 ml) were added. After stirring for 30 min., the pH was 5 adjusted to 6 and the layers were separated. The aqueous phase was extracted with ethyl acetate, the combined organic layers were washed with water, brine, dried (MgSO₄) and evaporated. The residue was triturated with ether, the precipitate filtered off and dried in vacuo to obtain the subtitled compound (3.5 g, 50%) as an off-white solid that was used without further purification. ¹H-NMR (DMSO-d₆) δ 1.15 (d, 10 *J* = 6.56 Hz, 6H), 3.51 (s, 2H), 4.04 (septet, *J* = 6.57 Hz, 1H), 6.76 (d, *J* = 7.65 Hz, 1H), 7.14 (d, *J* = 7.66 Hz, 1H), 7.27 (s, 1H), 7.84 (s, 2H), 10.41 (s, 1H).

10 A solution of (3,4-dihydro-4-isopropyl-2-oxoquinalin-6-yl)boronic acid (1.15 g, 4.9 mmol), 3-bromo-5-fluoro-benzonitrile (1.08 g, 5.4 mmol), potassium carbonate (2.75 g, 22 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.25 g, 15 0.2 mmol) in dimethoxyethane (70 ml), ethanol (15 ml) and water (15 mol) was heated to reflux for 6 hrs. After cooling to room temperature the mixture was concentrated and the residue was dissolved in ethyl acetate and 2N sodium hydroxide. The organic layer was washed with water, then brine, dried (MgSO₄) and evaporated. The residue was triturated with ether, and the precipitate was filtered off to afford the title 20 compound, mp 238-240 °C (0.5 g, 30%); ¹H-NMR (DMSO-d₆) δ 1.17 (d, *J* = 6.49 Hz, 6H), 3.59 (s, 1H), 4.30 (septet, *J* = 6.54 Hz, 1H), 6.89 (d, *J* = 8.00 Hz, 1H), 7.11 (d, *J* = 8.08 Hz, 1H), 7.76 (d, *J* = 8.34 Hz, 1H), 7.91 (d, *J* = 10.47 Hz, 1H), 8.06 (s, 1H), 10.56 (s, 1H). MS (ESI) m/z 308 [M-H]⁺.

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EXAMPLE 21

6-(3-Chloro-4-fluoro-phenyl)-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one

A mixture of (3,4-dihydro-4-isopropyl-2-oxoquinalin-6-yl)boronic acid (2.4 g, 10 mmol), 4-bromo-2-chlorofluorobenzene (2 g, 10 mmol), potassium carbonate (4 g, 30 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.46 g, 0.4 mmol) in

dimethoxyethane (100 ml), ethanol (25 ml) and water (25 mol) was heated to reflux for 6 hrs. After cooling to room temperature the mixture was diluted with water and extracted with ethyl acetate (3x). The combined organic layers were washed with water, then brine, dried ($MgSO_4$) and evaporated to obtain crude product (2.9 g, 91%). Recrystallization from EtOAc/hexane afforded the title compound, mp 208-213 °C: 1H -NMR (DMSO- d_6) δ 1.16 (d, J = 6.59 Hz, 6H), 3.56 (s, 2H), 4.22 (septet, J = 6.59 Hz, 1H), 6.86 (d, J = 7.91 Hz, 1H), 6.96 (dd, J = 7.91, 1.76 Hz, 1H), 7.01 (d, J = 1.76 Hz, 1H), 7.43 (t, J = 9.01 Hz, 1H), 7.61 (m, 1H), 7.82 (dd, J = 7.14, 2.31 Hz, 1H), 10.47 (s, 1H). MS (EI) m/z 318 [M] $^+$ + 1 chlorine.

10

EXAMPLE 22

6-(3-Chloro-phenyl)-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one

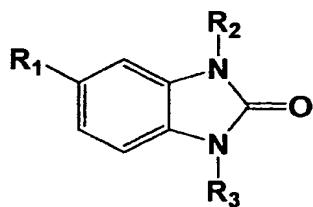
A mixture of 6-bromo-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one (2 g, 75 mmol), 3-chlorophenylboronic acid (1.6 g, 10 mmol), potassium carbonate (4g, 30 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.4 g, 0.35 mmol) in dimethoxyethane (100 ml), ethanol (25 ml), and water (25 ml) was heated to reflux for 6 hrs. After cooling to room temperature the mixture was diluted with water and extracted with EtOAc (3x50 mL). The combined organic layers were washed with water, then brine, dried ($MgSO_4$) and evaporated to give crude product (1.5 g, 66%). Recrystallization from EtOAc/hexane afforded the title compound: mp 146-150 °C. 1H -NMR (DMSO- d_6) δ 1.16 (d, J = 6.37 Hz, 6H), 3.57 (s, 2H), 4.21 (septet, J = 6.59 Hz, 1H), 6.87 (d, J = 7.91 Hz, 1H), 6.98 (dd, J = 7.91, 1.76 Hz, 1H), 7.02 (d, J = 1.76 Hz, 1H), 7.35 (m, 1H), 7.43 (t, J = 7.69 Hz, 1H), 7.57 (m, 1H), 7.66 (t, J = 1.76 Hz, 1H), 10.48 (s, 1H). MS (EI) m/z 300 (M) $^+$ + 1 chlorine.

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EXAMPLE 23 -Pharmacology

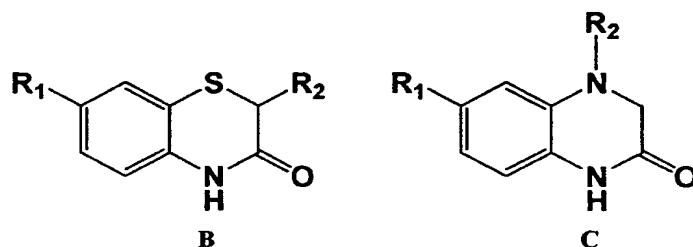
The compounds of this invention were tested in the relevant assay as described below and their potency are in the range of 0.01 nM to 5 mM in the *in vitro* assays and 0.001 to 300 mg/kg in the *in vivo* assays. The selected examples are listed in Table 1 and 2.

Table 1

				Alkaline Phosphatase	hPR	CV-1
	Compound	R ₁	R ₂	R ₃	IC ₅₀ (nM)	IC ₅₀ (nM)
10	1	3-chlorophenyl	Bn	H		412
15	2	3-nitrophenyl	Bn	H		230
20	3	3-chlorophenyl phenyl	Me	H		1370
	4	3-nitrophenyl	Me	H		1529
	5	3-nitrophenyl	H	Me		750
25	6	3-nitrophenyl	isopropyl	H		147
	7	3-chlorophenyl	isopropyl	H		155

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Table 2



5	Compound	R ₁	R ₂	Alkaline Phosphatase	
				IC ₅₀ (nM)	hPR CV-1
10	B1	3-nitrophenyl	H		220
	B2	3-nitrophenyl	Et		295
15	C1	3-chlorophenyl	Me	600	1585
	C2	3-chlorophenyl	H	550	525
20	C3	2-(4-cyanothio-phenyl)	Me	300	
	C4	3-chlorophenyl	isopropyl	850	
25	C5	3-chloro-4-fluoro-phenyl	isopropyl	700	
	C6	3-chlorophenyl	n-Bu	500	

1. T47D cell proliferation assay

The objective of this assay is the determination of progestational and antiprogestational potency by using a cell proliferation assay in T47D cells. A compound's effect on DNA synthesis in T47D cells is measured. The 5 materials and methods used in this assay are as follows.

a. Growth medium: DMEM:F12 (1:1)

(GIBCO, BRL) supplemented with 10% (v/v) fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

10 b. Treatment medium: Minimum Essential Medium (MEM) (#51200-038GIBCO, BRL) phenol red-free supplemented with 0.5% charcoal stripped fetal bovine serum, 100U/ml penicillin, 200 mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

c. Cell culture

15 Stock T47 D cells are maintained in growth medium. For BrdU incorporation assay, cells are plated in 96-well plates (Falcon, Becton Dickinson Labware) at 10,000 cells/well in growth medium. After overnight incubation, the medium is changed to treatment medium and cells are cultured for an additional 24 hr before treatment.

20 Stock compounds are dissolved in appropriate vehicle (100% ethanol or 50% ethanol/50% DMSO), subsequently diluted in treatment medium and added to the cells. Progestin and antiprogestin reference compounds are run in full dose-response curves. The final concentration of vehicle is 0.1%. In control wells, cells receive vehicle only. Antiprogestins are tested in the presence of 0.03 nM trimegestone, the reference progestin agonist. Twenty-four hours after treatment, the medium is 25 discarded and cells are labeled with 10 mM BrdU (Amersham Life Science, Arlington Heights, IL) in treatment medium for 4 hr.

d. Cell Proliferation Assay

At the end of BrdU labeling, the medium is removed and BrdU incorporation is measured using a cell proliferation ELISA kit (#RPN 250, Amersham

Life Science) according to manufacturer's instructions. Briefly, cells are fixed in an ethanol containing fixative for 30 min, followed by incubation in a blocking buffer for 30 min to reduce background. Peroxidase-labeled anti-BrdU antibody is added to the wells and incubated for 60 min. The cells are rinsed three times with PBS and 5 incubated with 3,3'5,5'-tetramethylbenzidine (TMB) substrate for 10-20 min depending upon the potency of tested compounds. Then 25 μ l of 1 M sulfuric acid is added to each well to stop color reaction and optical density is read in a plate reader at 450 nm within 5 min.

e. Analysis of Results:

10 Square root-transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC₅₀ or IC₅₀ values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose 15 response studies.

f. Reference Compounds:

Trimegestone and medroxyprogesterone acetate (MPA) are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the EC₅₀ or IC₅₀ values are calculated.

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Table 3. Estimated EC₅₀, standard error (SE), and 95% confidence intervals (CI) for individual studies

5	<u>Compound</u>	<u>Exp</u>	<u>EC₅₀</u>	<u>95% CI</u>		
			(nM)	SE	lower	upper
10	Trimegestone	1	0.017	0.003	0.007	0.040
		2	0.014	0.001	0.011	0.017
		3	0.019	0.001	0.016	0.024
15	MPA	1	0.019	0.001	0.013	0.027
		2	0.017	0.001	0.011	0.024

Table 4. Estimated IC₅₀, standard error, and 95% confident interval for the antiprogestin, RU486

	<u>Compound</u>	<u>Exp</u>	<u>IC₅₀</u>	<u>95% CI</u>		
			(nM)	SE	lower	upper
20	RU486	1	0.011	0.001	0.008	0.014
		2	0.016	0.001	0.014	0.020
		3	0.018	0.001	0.014	0.022

EC₅₀: Concentration of a compound that gives half-maximal increase in BrdU incorporation with SE; IC₅₀: Concentration of a compound that gives half-maximal decrease in 0.1 trimegestone induced BrdU incorporation with SE

2. Rat decidualization assay

The objective of this procedure is used to evaluate the effect of progestins and antiprogestins on rat uterine decidualization and compare the relative potencies of various test compounds. The materials and methods used in this assay are as follows.

5 a. Methods: Test compounds are dissolved in 100% ethanol and mixed with corn oil (vehicle). Stock solutions of the test compounds in oil (MazolaTM) are then prepared by heating (~80 °C) the mixture to evaporate ethanol. Test compounds are subsequently diluted with 100% corn oil or 10% ethanol in corn oil prior to the treatment of animals. No difference in decidual response was found when these two vehicles were compared.

b. Animals (RACUC protocol #5002)

10 Ovariectomized mature female Sprague-Dawley rats (~60-day old and 230g) are obtained from Taconic (Taconic Farms, NY) following surgery. Ovariectomy is performed at least 10 days prior to treatment to reduce circulating sex steroids. Animals are housed under 12 hr light/dark cycle and given standard rat chow and water *ad libitum*.

c. Treatment

15 Rats are weighed and randomly assigned to groups of 4 or 5 before treatment. Test compounds in 0.2 ml vehicle are administered by subcutaneous injection in the nape of the neck or by gavage using 0.5 ml. The animals are treated once daily for seven days. For testing antiprogestins, animals are given the test compounds and a EC50 dose of progesterone (5.6 mg/kg) during the first three days of treatment. Following decidual stimulation, animals continue to receive 20 progesterone until necropsy four days later.

d. Dosing

25 Doses are prepared based upon mg/kg mean group body weight. In all studies, a control group receiving vehicle is included. Determination of dose-response curves is carried out using doses with half log increases (e.g. 0.1, 0.3, 1.0, 3.0 mg/kg...).

e. Decidual induction

Approximately 24 hr after the third injection, decidualization is induced in one of the uterine horns by scratching the antimesometrial luminal epithelium with a blunt 21 G needle. The contralateral horn is not scratched and serves

as an unstimulated control. Approximately 24 hr following the final treatment, rats are sacrificed by CO₂ asphyxiation and body weight measured. Uteri are removed and trimmed of fat. Decidualized (D-horn) and control (C-horn) uterine horns are weighed separately.

5 f. Analysis of Results:

The increase in weight of the decidualized uterine horn is calculated by D-horn/C-horn and logarithmic transformation is used to maximize normality and homogeneity of variance. The Huber M-estimator is used to down weight the outlying transformed observations for both dose-response curve fitting and 10 one-way analysis of variance. JMP software (SAS Institute, Inc.) is used for both one-way ANOVA and non-linear dose-response analyses.

g. Reference Compounds:

All progestin reference compounds were run in full dose-response curves and the EC₅₀ for uterine wet weight were calculated.

15 **Table 5. Estimated EC₅₀, standard error (SE), and 95% confidence intervals for individual studies**

Compound	Exp	EC ₅₀ (mg/kg, s.c.)	95% CI		
			SE	lower	upper
Progesterone	1	5.50	0.77	4.21	7.20
	2	6.21	1.12	4.41	8.76
3-Ketodesogestrel	1	0.11	0.02	0.07	0.16
	2	0.10	0.05	0.11	0.25
	3	0.06	0.03	0.03	0.14
Levonorgestrel	1	0.08	0.03	0.04	0.16
	2	0.12	0.02	0.09	0.17
	3	0.09	0.02	0.06	0.13
	4	0.09	0.02	0.06	0.14

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MPA	1	0.42	0.03	0.29	0.60
	2	0.39	0.05	0.22	0.67
	3	0.39	0.04	0.25	0.61

5 **Table 6. Estimated average EC₅₀, standard error, and 95% confidence intervals for dose-response curves of 3 reference compounds**

	Compound	EC ₅₀		95% CI	
		(mg/kg, s.c.)	SE	lower	upper
10	Progesterone	5.62	0.62	4.55	7.00
	3-Ketodesogestrel	0.10	0.02	0.07	0.14
	Levonorgestrel	0.10	0.01	0.08	0.12

15 **Table 7. Estimated IC₅₀, standard error, and 95% confident interval for the antiprogestin, RU 486**

	Compound	IC ₅₀		95% CI	
		Exp.	(mg/kg, p.o.)	SE	lower upper
20	RU 486	1	0.21	0.07	0.05 0.96
		2	0.14	0.02	0.08 0.27

Concentration: Compound concentration in assay(default-mg/kg body weight)

Route of administration: Route the compound is administered to the animals

25 Body weight: Mean total animal body weight (default-kg)

D-horn: Wet weight of decidualized uterine horn (default-mg)

C-horn: Wet weight of control uterine horn (default-mg)

Decidual response: [(D-C)/C]x100%

30 Progestational activity: Compounds that induce decidualization significantly (p<0.05) compared to vehicle control are considered active

Antiprogestational activity: Compounds that decrease EC₅₀ progesterone induced decidualization significantly (p<0.05)

EC₅₀ for uterine weight: Concentration of compound that gives half-maximal increase in decidual response (default-mg/kg)

5 IC₅₀ for uterine weight: Concentration of compound that gives half-maximal decrease in EC₅₀ progesterone induced decidual response (default-mg/kg)

3. PRE-luciferase assay in CV-1 cells

10 The object of this assay is to determine a compound's progestational or antiprogestational potency based on its effect on PRE-luciferase reporter activity in CV-1 cells co-transfected with human PR and PRE-luciferase plasmids. The materials methods used in the assay are as follows.

15 a. Growth medium: DMEM (BioWhittaker) containing 10% (v/v) fetal bovine serum (heat inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL). Experimental medium: DMEM (BioWhittaker), phenol red-free, containing 10% (v/v) charcoal-stripped fetal bovine serum (heat-inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

20 b. Cell culture, transfection, treatment, and luciferase assay

Stock CV-1 cells are maintained in growth medium. Co-transfection is done using 1.2x10⁷ cells, 5 mg pLEM plasmid with hPR-B inserted at SphI and BamH1 sites, 10 mg pGL3 plasmid with two PREs upstream of the luciferase sequence, and 50 mg sonicated calf thymus DNA as carrier DNA in 250 ml. 25 Electroporation is carried out at 260 V and 1,000 mF in a Biorad Gene Pulser II. After electroporation, cells are resuspended in growth medium and plated in 96-well plate at 40,000 cells/well in 200 μ l. Following overnight incubation, the medium is changed to experimental medium. Cells are then treated with reference or test compounds in experimental medium. Compounds are tested for antiprogestational

activity in the presence of 3 nM progesterone. Twenty-four hr. after treatment, the medium is discarded, cells are washed three times with D-PBS (GIBCO, BRL). Fifty μ l of cell lysis buffer (Promega, Madison, WI) is added to each well and the plates are shaken for 15 min in a Titer Plate Shaker (Lab Line Instrument, Inc.). Luciferase

5 activity is measured using luciferase reagents from Promega.

c. Analysis of Results:

Each treatment consists of at least 4 replicates. Log transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight 10 the effects of outliers. EC₅₀ or IC₅₀ values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear response analyses.

d. Reference Compounds:

Progesterone and trimegestone are reference progestins and 15 RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the EC₅₀ or IC₅₀ values are calculated.

Table 8. Estimated EC₅₀, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three individual studies

20

Compound	Exp.	EC ₅₀		95% CI	
		(nM)	SE	lower	upper
Progesterone	1	0.616	0.026	0.509	0.746
	2	0.402	0.019	0.323	0.501
	3	0.486	0.028	0.371	0.637
Trimegestone	1	0.0075	0.0002	0.0066	0.0085
	2	0.0081	0.0003	0.0070	0.0094
	3	0.0067	0.0003	0.0055	0.0082

30

Table 9. Estimated IC₅₀, standard error (SE), and 95% confident interval (CI) for the antiprogestin, RU486 from three individual studies

5	Compound	Exp.	<u>IC 50</u>		<u>95% CI</u>	
			(nM)	SE	lower	upper
10	RU486	1	0.028	0.002	0.019	0.042
		2	0.037	0.002	0.029	0.048
		3	0.019	0.001	0.013	0.027

10 Progestational activity: Compounds that increase PRE-luciferase activity significantly (p<0.05) compared to vehicle control are considered active.

Antiprogestational activity: Compounds that decrease 3 nM progesterone induced PRE-luciferase activity significantly (p<0.05)

15 EC₅₀: Concentration of a compound that gives half-maximal increase PRE-luciferase activity (default-nM) with SE.

IC₅₀: Concentration of a compound that gives half-maximal decrease in 3 nM progesterone induced PRE-luciferase activity (default-nM) with SE.

4. T47D cell alkaline phosphatase assay

20 The purpose of this assay is to identify progestins or antiprogestins by determining a compound's effect on alkaline phosphatase activity in T47D cells. The materials and methods used in this assay are as follows.

a. Culture medium: DMEM:F12 (1:1) (GIBCO, BRL) supplemented with 5% (v/v) charcoal stripped fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100 µg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

25 b. Alkaline phosphatase assay buffer:

I. 0.1 M Tris-HCl, pH 9.8, containing 0.2% Triton X-100

II. 0.1 M Tris-HCl, pH 9.8 containing 4 mM p-nitrophenyl phosphate (Sigma).

c. Cell Culture and Treatment:

Frozen T47D cells were thawed in a 37°C water bath and diluted to 280,000 cells/ml in culture medium. To each well in a 96-well plate (Falcon, Becton Dickinson Labware), 180 μ l of diluted cell suspension was added.

5 Twenty μ l of reference or test compounds diluted in the culture medium was then added to each well. When testing for progestin antagonist activity, reference antiprogestins or test compounds were added in the presence of 1 nM progesterone. The cells were incubated at 37°C in a 5% CO₂/humidified atmosphere for 24 hr.

d. Alkaline Phosphatase Enzyme Assay:

10 At the end of treatment, the medium was removed from the plate and fifty μ l of assay buffer I was added to each well. The plates were shaken in a titer plate shaker for 15 min. Then 150 μ l of assay buffer II was added to each well. Optical density measurements were taken at 5 min intervals for 30 min at a test wavelength of 405 nM.

15 e. Analysis of Results: Analysis of dose-response data

For reference and test compounds, a dose response curve is generated for dose (X-axis) vs. the rate of enzyme reaction (slope) (Y-axis). Square root-transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to 20 downweight the effects of outliers. EC₅₀ or IC₅₀ values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose response studies.

f. Reference Compounds:

25 Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose response curves and the EC₅₀ or IC₅₀ values are calculated.

Table 10. Estimated EC₅₀, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three independent experiments

	Compound	Exp.	EC ₅₀ (nM)	SE	95% CI lower	95% CI upper
5	Progesterone	1	0.839	0.030	0.706	0.996
		2	0.639	0.006	0.611	0.669
	10	3	1.286	0.029	1.158	1.429
15	Trimegestone	1	0.084	0.002	0.076	0.091
		2	0.076	0.001	0.072	0.080
		3	0.160	0.004	0.141	0.181

Table 11. Estimated IC₅₀, standard error, and 95% confident interval for the reference antiprogestin RU486 from three independent experiments

	Compound	Exp	IC 50 (nM)	SE	95% CI lower	95% CI upper
20	RU486	1	0.103	0.002	0.092	0.115
		2	0.120	0.001	0.115	0.126
		3	0.094	0.007	0.066	0.134

EXAMPLE 24

1-Benzyl-6-(3-chlorophenyl)-1,3-dihydro-2H-benzimidazole-2-thione

To a solution of 1-benzyl-6-(3-chlorophenyl)-1,3-dihydro-2H-benzimidazole-2-thione (0.1g, 0.3 mmol) in anhydrous toluene was added under a blanket of nitrogen Lawesson's reagent (0.133g, 0.33 mmol). The mixture was heated to 110 °C under nitrogen for 3 hours, allowed to cool to ambient temperature, and the solvent was

removed. The residue was purified by a silica gel chromatography (hexane:ethyl acetate/5:1) to give the title compound as a yellow solid (0.03g, 29%): mp 211-212 °C; ¹H-NMR (DMSO-d₆) δ 12.99 (s, 1H), 7.70 (t, 1H, J = 1.7 Hz), 7.64 (m, 1H), 7.58-7.61 (m, 1H), 7.25-7.54 (m, 9H), 5.59 (s, 2H); MS (ESI) m/z 349 [M - H]⁺; 5 Anal. Calc. For C₂₀H₁₅ClN₂S: C, 68.46, H, 4.31, N, 7.98. Found: C, 68.07, H, 4.23, N, 7.88.

EXAMPLE 25

1-Benzyl-6-(3-nitrophenyl)-1,3-dihydro-2H-benzimidazole-2-thione

10 Prepared according to the procedure for Example 24 from 1-benzyl-6-(3-nitrophenyl)-1,3-dihydro-2H-benzimidazole-2-one (0.1g, 0.29 mmol) and Lawesson's reagent (0.13g, 0.32 mmol). A yellow solid (0.025g, 24%): mp 244-245 °C; ¹H-NMR (DMSO-d₆) δ 13.08 (s, 1H), 8.43 (s, 1H), 8.20 (dd, 1H, J = 8.2, 1.7 Hz), 8.12 (d, 1H, J = 7.8 Hz), 7.72-7.78 (m, 2H), 7.62 (d, 1H, J = 8.3 Hz), 7.25-7.43 (m, 6H), 5.62 (s, 2H); MS (ESI) m/z 360 [M - H]⁺; Anal. Calc. For C₂₀H₁₅ClN₂S•0.2H₂O: C, 65.81, H, 4.25, N, 11.51. Found: C, 65.56, H, 4.11, N, 11.29.

EXAMPLE 26

6-(3-Nitro-phenyl)-4-methyl-3,4-dihydro-1H-quinoxalin-2-one

20 Prepared according to the procedure for Example 5 from 6-bromo-4-methyl-3,4-dihydro-1H-quinoxalin-2-one (4.8 g, 20 mmol), and 3-nitrophenylboronic acid (4.8 g, 30 mmol). A red powder (0.95 g, 16%): mp 237-243 °C. ¹H-NMR (DMSO-d₆) δ 2.88 (s, 3H), 6.9 (d, J = 7.9 Hz, 1H), 7.01 (d, J = 2 Hz, 1H), 7.11 (dd, J = 7.9, 2.0 Hz, 1H), 7.7 (t, J = 7.9 Hz, 1H), 8.1 (m, 2H), 8.37 (t, J = 0.7 Hz), MS (ESI) m/z 25

283 (M)⁺

EXAMPLE 27

6-(4-Chloro-phenyl)-3-methyl-3,4-dihydro-1H-quinoxalin-2-one

A mixture of 4-bromo-2-fluoro-1-nitro-benzene (22 g, 100mmol), L-alanine (8.9 g, 100 mmol), and potassium carbonate (17.5 g, 125 mmol) in ethanol (250 ml), 5 and water (200 ml) was heated to reflux for 5 hours. After cooling to room temperature, the mixture was diluted with water, and acidified with 1N hydrochloric acid. The precipitate was collected on a funnel and dried to afford N-(5-bromo-2-nitrophenyl)-alanine (28.9 g, 100%). A sample was recrystallized from ethanol: m.p. 183-187 °C; ¹H-NMR (DMSO -d₆) δ 1.44 (d, *J* = 6.9 Hz, 3H), 4.56 (m, 1H), 6.87 (d, 10 *J* = 6 Hz, 1H), 7.21 (d, *J* = 1.7 Hz, 1H), 7.99 (d, *J* = 7 Hz, 1H), 8.36 (d, *J* = 7 Hz, 1H), 13.27 (s, 1H).

To a solution of N-(5-bromo-2-nitrophenyl)-alanine (22 g, 76 mmol) in acetic acid (300 ml) was added iron powder (10 g, 180 mmol), and the mixture was stirred for 2 hours at 90 °C. The reaction mixture was cooled and filtered, and the acetic acid 15 was evaporated. The remaining slurry was extracted with methylene chloride (3 x 200 ml). The combined extracts were combined, dried over magnesium sulfate, filtered, and evaporated to afford 6-bromo-3-methyl-3,4-dihydro-1H-quinoxalin-2-one (9.4 g, 51 %). A sample was recrystallized from ethanol: m.p. 133-135 °C. ¹H-NMR (DMSO-d₆) δ 1.23 (d, *J* = 6.81 Hz, 3H), 3.80 (q, *J* = 6.81 Hz, 1H), 6.27 (bs, 1H), 20 6.63 (d, *J* = 8.35 Hz, 1H), 6.72 (dd, *J* = 8.35, 1.76 Hz, 1H), 6.80 (d, *J* = 1.76 Hz, 1H), 10.29 (s, 1H).

A solution of 6-bromo-3-methyl-3,4-dihydro-1H-quinoxalin-2-one (2.4 g, 10 mmol), 4-chlorophenyl boronic acid (1.6 g, 10 mmol), potassium carbonate (4 g, 30 mmol), and tetrakis-(triphenylphosphine)palladium (0) in dimethoxyethane (150 ml), 25 ethanol (25 ml), and water (25 ml) was heated to reflux for 6 hours. After cooling to room temperature the mixture was diluted with water, and extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated to obtain crude product (0.83 g, 30 %). A sample was recrystallized from ethanol to afford the title compound: m.p. 228-230 °C. ¹H-NMR (DMSO-d₆) δ 1.28

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(d, $J = 6.63$ Hz, 3H), 3.83 (q, $J = 6.63$ Hz, 1H), 6.16 (bs, 1H), 6.81 (d, $J = 8.00$ Hz, 1H), 6.91 (dd, $J = 8.05, 1.9$ Hz, 1H), 6.95 (d, $J = 1.7$ Hz, 1H), 7.46 (d, $J = 8.6$ Hz, 2H), 7.55 (d, $J = 8.6$ Hz, 2H), 10.32 (s, 1H); MS (EI) m/z 272/274.

5

EXAMPLE 28

4-Benzyl-6-(3-chlorophenyl)-3,4-dihydroquinoxalin-2(1H)-one

In a manner as described above, 4-bromo-2-fluoro-1-nitro-benzene (11 g, 50 mmol), and N-benzyl-glycine ethyl ester (10 g, 50 mmol) were reacted to give crude [(5-bromo-nitro-phenyl)-benzyl-amino]-acetic acid (10 g, 55 %). This product was 10 reacted with iron powder to obtain crude 4-benzyl-6-bromo-3,4-dihydroquinoxalin-2(1H)-one (5 g, 58 %). A sample was recrystallized from ethyl acetate/hexane: m.p. 174-176 °C. 1 H-NMR (DMSO-d₆) δ 3.75 (s, 2H), 4.43 (s, 2H), 6.71 (d, $J = 1.9$ Hz, 1H), 6.81 (m, 2H), 7.32 (m, 5H), 10.57 (s, 1H).

The title compound was prepared according to the procedure for Example 5 15 from 4-benzyl-6-bromo-3,4-dihydroquinoxalin-2(1H)-one (1.6 g, 5 mmol), and 3-chlorophenyl boronic acid (0.8 g, 5 mmol). An off-white powder (0.9 g, 51 %): m.p. 182-185 °C. 1 H-NMR (DMSO-d₆) δ 3.74 (s, 2H), 4.54 (s, 2H), 6.87 (d, $J = 0.7$ Hz), 7.0 (m, 2H), 7.36 (m, 8H), 7.52 (t, $J = 1.8$ Hz, 1H), 10.57 (s, 1H), MS (ESI) m/z 349 (M+H)⁺

20

EXAMPLE 29

Isopropyl 7-(3-chlorophenyl)-3-oxo-3,4-dihydroquinoxalin-1(2H)-carboxylate

To a solution of 7-bromo-3-oxo-3,4-dihydroquinoxaline (6.8 g, 30 mmol) in pyridine (50 ml) was added a solution of isopropyl chloroformate in toluene (35 ml, 25 1M, 35 mmol) over 30 minutes. The mixture was triturated with water/chloroform, the organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated to obtain crude isopropyl 7-bromo-3-oxo-3,4-dihydroquinoxaline-1(2H)-carboxylate (9.3 g, 97 %). A sample was recrystallized from ethanol: m.p. 159-161 °C. 1 H-NMR (DMSO-d₆) δ 1.25 (d, $J = 6.2$ Hz, 6H), 4.25 (s, 2H), 4.90 (sep, $J = 6.2$ Hz,

1H), 6.89 (d, J = 8.6 Hz, 1H), 7.27 (dd, J = 9.1, 2.1 Hz, 1H), 7.74 (s, 1H), 12.51 (s, 1H), MS (ESI) m/z 330/332 (M+NH₄)⁺.

The title compound was prepared according to the procedure for Example 5 from isopropyl 7-bromo-3-oxo-3,4-dihydroquinoxaline-1(2H)-carboxylate (6.3 g, 20 mmol), and 3-chlorophenyl boronic acid (3.2 g, 20 mmol). Off-white crystals (3.7 g, 49 %): m.p. 174-176 °C. ¹H-NMR (DMSO-d₆) δ 1.27 (d, J = 6.4 Hz, 6H), 4.30 (s, 2H), 4.94 (sep, J = 6.2 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 7.50 (m, 4H), 7.61 (t, J = 1.9 Hz, 1H), 7.86 (s, 1H), 10.79 (s, 1H), MS(APCI) m/z 345/347 (M+H)⁺.

10

EXAMPLE 30

Isopropyl 7-(3-chlorophenyl)-3-thioxo-3,4-dihydroquinoxaline-1(2H)-carboxylate

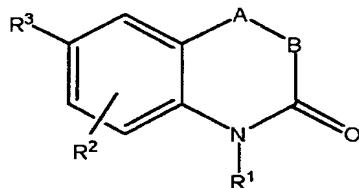
Prepared according to the procedure for Example 24 from isopropyl 7-(3-chlorophenyl)-3-oxo-3,4-dihydroquinoxaline-1(2H)-carboxylate and Lawesson's reagent. A yellowish solid: m.p. 208-212 °C; ¹H-NMR (DMSO-d₆) δ 1.27 (d, J = 6.1 Hz, 6H), 4.62 (s, 2H), 4.94 (sep, J = 6.1 Hz, 1H), 7.23 (m, 4H), 7.64 (t, J = 1.8 Hz, 1H), 7.90 (s, 1H), 12.80 (s, 1H), MS (ESI) m/z 359/361 (M-H)⁻.

20 All publications cited in this specification are incorporated herein by reference herein. While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

What is Claimed:

1. A method of contraception which comprises administering to a female of child bearing age for 28 consecutive days:

- a) a first phase of from 14 to 24 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 μ g levonorgestrel;
- b) a second phase of from 1 to 11 daily dosage units, at a daily dosage of from about 2 to 50 mg, of an antiprogestin compound of Formula 1:



wherein:

A is O, S, or NR⁴;

B is a bond between A and C=Q, or the moiety CR⁵R⁶;

R⁴, R⁵, R⁶ are independently selected from H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, cyclic alkyl constructed by fusing R⁴ and R⁵ to from a 5 to 7 membered ring;

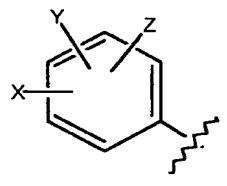
R¹ is selected from H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, alkynyl, substituted alkynyl, or COR^A;

R^A is selected from H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^2 is selected from H, halogen, CN, NO₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, C₁ to C₆ aminoalkyl, or substituted C₁ to C₆ aminoalkyl;

R^3 is selected from a) or b):

a) R^3 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



X is selected from the group of halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^B, OCOR^B, or NR^CCOR^B,

R^B is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^C is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkoxy;

or

b) R³ is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O S, SO, SO₂ or NR⁷ and containing one or two independent substituents from the group of H, halogen, CN, NO₂ and C₁ to C₃ alkyl, C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, COR^D, or NR^ECOR^D;

R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

R⁷ is H, or C₁ to C₃ alkyl;

or a pharmaceutically acceptable salt thereof; and

c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo for the remaining days of the 28 consecutive days in which no antiprogestin, progestin or estrogen is administered; wherein the total daily dosage units of the first, second and third phases equals 28.

2. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure of Formula 1 in Claim 1 wherein:

A is O, S, or NR⁴;

B is a bond between A and C=Q, or the moiety CR⁵R⁶;

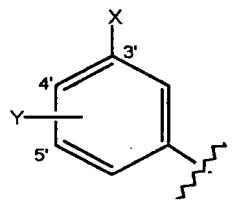
R^4 , R^5 , R^6 are independent substituents from the group including H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, or cyclic alkyl constructed by fusing R⁴ and R⁵ to from a 5 to 7 membered ring;

R^1 is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, or COR^A;

R^A is H, C₁ to C₄ alkyl, C₁ to C₄ alkoxy;

R^2 is H, halogen, NO₂, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

R^3 is a disubstituted benzene ring containing the substituents X and Y as shown below



X is taken from the group of halogen, CN, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, or C₁ to C₃ thioalkoxy;

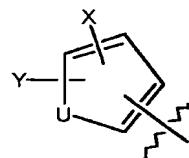
Y is a substituent on the 4' or 5' position from the group of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₄ alkyl, or C₁ to C₃ thioalkoxy;

or a pharmaceutically acceptable salt thereof.

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3. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure of Formula 1 in Claim 1 wherein:

R^3 is a five membered ring with the structure:



U is O, S, or NR^7 ;

R^7 is H, C_1 to C_3 alkyl, or C_1 to C_4 CO_2 alkyl;

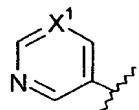
X' is selected from the group of halogen, CN, NO_2 , C_1 to C_3 alkyl or C_1 to C_3 alkoxy;

Y' is H or C_1 to C_4 alkyl; and

A , B , R^1 , R^2 , R^4 , R^5 , and R^6 are as defined in Claim 2; or a pharmaceutically acceptable salt thereof.

4. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure of Formula 1 in Claim 1 wherein:

R^3 is a six membered ring with the structure:

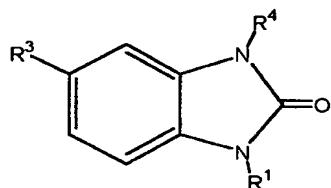


X^1 is N or CX^2 ;

X^2 is halogen, CN or NO_2 ; and

A, B, R¹, R², R⁴, R⁵, and R⁶ are as defined in Claim 2; or a pharmaceutically acceptable salt thereof.

5. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure of Formula 1 in Claim 1 wherein:



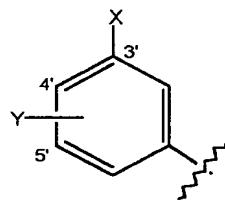
wherein:

R¹ is selected from H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, alkynyl, substituted alkynyl, or COR^A;

R^A is selected from H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R⁴ is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, benzyl, or substituted benzyl; and

R³ is selected from halogen or a disubstituted benzene ring containing the substituents X and Y as shown below



X is taken from the group of halogen, CN, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, NO₂, C₁ to C₃ perfluoroalkyl, or C₁ to C₃ thioalkoxy;

Y is a substituent on the 4' or 5' position from the group of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₄ alkyl, or C₁ to C₃ thioalkoxy; or a pharmaceutically acceptable salt thereof.

6. A method of Claim 1 wherein the antiprogestin compound is 5-Bromo-2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid *tert*-butyl ester or a pharmaceutically acceptable salt thereof.

7. A method of Claim 1 wherein the antiprogestin compound is 1-Benzyl-6-bromo-1,3-dihydro-benzoimidazol-2-one or a pharmaceutically acceptable salt thereof.

8. A method of Claim 1 wherein the antiprogestin compound is 5-Bromo-3-methyl-2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid *tert*-butyl ester or a pharmaceutically acceptable salt thereof.

9. A method of Claim 1 wherein the antiprogestin compound is 6-Bromo-1-methyl-1,3-dihydro-benzoimidazol-2-one or a pharmaceutically acceptable salt thereof.

10. A method of Claim 1 wherein the antiprogestin compound is 1-Benzyl-6-(3-chloro-phenyl)-1,3-dihydro-benzoimidazol-2-one or a pharmaceutically acceptable salt thereof.

11. A method of Claim 1 wherein the antiprogestin compound is 1-Benzyl-6-(3-nitro-phenyl)-1,3-dihydro-benzimidazol-2-one or a pharmaceutically acceptable salt thereof.

12. A method of Claim 1 wherein the antiprogestin compound is 1-Methyl-6-(3-nitro-phenyl)-1, 3-dihydro-benzimidazol-2-one or a pharmaceutically acceptable salt thereof.

13. A method of Claim 1 wherein the antiprogestin compound is 6-(3-chloro-phenyl)-1-methyl-1,3-dihydro-benzimidazol-2-one or a pharmaceutically acceptable salt thereof.

14. A method of Claim 1 wherein the antiprogestin compound is 5-(3-Nitro-phenyl)-1,3-dihydro-benzimidazol-2-one or a pharmaceutically acceptable salt thereof.

15. A method of Claim 1 wherein the antiprogestin compound is 4-Amino-3'-nitro-biphenyl-3-ol or a pharmaceutically acceptable salt thereof.

16. A method of Claim 1 wherein the antiprogestin compound is 6-(3-Nitro-phenyl)-3H-benzooxazol-2-one or a pharmaceutically acceptable salt thereof.

17. A method of Claim 1 wherein the antiprogestin compound is 6-(3-Nitro-phenyl)-3H-benzothiazol-2-one or a pharmaceutically acceptable salt thereof.

18. A method of Claim 1 wherein the antiprogestin compound is 6-(3-Chloro-phenyl)-3H-benzothiazol-2-one or a pharmaceutically acceptable salt thereof.

19. A method of Claim 1 wherein the antiprogestin compound is 7-(3-Nitro-phenyl)-4H-benzo[1,4]thiazin-3-one or a pharmaceutically acceptable salt thereof.

20. A method of Claim 1 wherein the antiprogestin compound is 2-Ethyl-7-(3-nitro-phenyl)-4H-benzo[1,4]thiazin-3-one or a pharmaceutically acceptable salt thereof.

21. A method of Claim 1 wherein the antiprogestin compound is 8-(3-Chloro-phenyl)-1,2,3,3a-tetrahydro-5H-pyrrolo[1,2-a]quinoxalin-4-one or a pharmaceutically acceptable salt thereof.

22. A method of Claim 1 wherein the antiprogestin compound is 6-(3-Chloro-phenyl)-4-methyl-3,4-dihydro-1H-quinoxalin-4-one or a pharmaceutically acceptable salt thereof.

23. A method of Claim 1 wherein the antiprogestin compound is 5-(3, 4-Dihydro-4-methyl-2-oxo-quinaxalin-6-yl) thiophene-3-carbonitrile or a pharmaceutically acceptable salt thereof.

24. A method of Claim 1 wherein the antiprogestin compound is 4-(*n*-Butyl)-6-(3-chloro-phenyl)-3,4-dihydro-1H quinoxalin-2-one [(5-Bromo-2-nitro-phenyl)-*n*-butyl-amino]acetic acid or a pharmaceutically acceptable salt thereof.

25. A method of Claim 1 wherein the antiprogestin compound is 6-(3-Cyano-5-fluorophenyl)-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one or a pharmaceutically acceptable salt thereof.

26. A method of Claim 1 wherein the antiprogestin compound is 6-(3-Chloro-4-fluoro-phenyl)-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one or a pharmaceutically acceptable salt thereof.

27. A method of Claim 1 wherein the antiprogestin compound is 6-(3-Chloro-phenyl)-4-isopropyl-3,4-dihydro-1H-quinoxalin-2-one or a pharmaceutically acceptable salt thereof.

28. The method of Claim 1 wherein the progestational agent is selected from the group of levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, nomegestrol, or (17-deacetyl)norgestimate.

29. A method of Claim 1 which comprises administering to a female of child bearing age consecutively over a 28 day cycle:

- a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 µg levonorgestrel;
- b) a second phase of 3 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and
- c) optionally, 4 daily dosage units of an orally and pharmaceutically acceptable placebo to be administered on each day of the 28-day cycle following the first phase and second phase.

30. A method of contraception which comprises administering to a female of child bearing age over a period of 28 consecutive days:

- a) a first phase of from 18 to 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and
- b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and
- c) optionally, an orally and pharmaceutically acceptable placebo for each remaining day of the 28 consecutive days.

31. A method of contraception of Claim 30 which comprises administering to a female of child bearing age over a period of 28 consecutive days:

- a) a first phase of 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 100 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and
- b) a second phase of 3 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and
- c) optionally, a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

32. A method of contraception which comprises administering to a female of child bearing age over a period of 28 consecutive days:

- a) a first phase of from 18 to 21 daily dosage units containing a progestational agent at a daily dose equal in progestational activity to from about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg
- b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and
- c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo, the total of the daily dosage units being 28.

33. A method of contraception of Claim 32 which comprises administering to a female of child bearing age over a period of 28 consecutive days:

- a) a first phase of 21 daily dosage units, each daily dosage unit containing a progestational agent at a daily dose equal in progestational activity to about 35 to about 100 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg
- b) a second phase of 3 daily dose, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and
- c) optionally, a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

34. A pharmaceutically useful kit adapted for daily oral administration which comprises:

- a) a first phase of from 14 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel;
- b) a second phase of from 1 to 11 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg, and
- c) a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

35. A pharmaceutically useful kit adapted for daily oral administration of Claim 34 which comprises:

- a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel;

- b) a second phase of 3 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and
- c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

36. A pharmaceutically useful kit adapted for daily oral administration which comprises:

- a) a first phase of from 18 to 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and
- b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and
- c) a third phase of from 0 to 9 daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

37. A pharmaceutically useful kit adapted for daily oral administration of Claim 36 which comprises:

- a) a first phase of 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and
- b) a second phase of three daily dosage units of an antiprogestin of Claim 1 administered at a daily dose of from about 2 to 50 mg; and
- c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

38. A pharmaceutically useful kit adapted for daily oral administration which comprises:

- a) a first phase of from 18 to 21 daily dosage units, each daily dosage unit comprising a progestational agent at a daily dose equal in progestational activity to from about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg
- b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and
- c) a third phase of from 0 to 9 daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

39. A pharmaceutically useful kit adapted for daily oral administration of Claim 38 which comprises:

- a) a first phase of 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 µg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg
- b) a second phase of 3 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 µg; and
- c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER		
IPC 7 A61K45/06 A61K31/57 A61P15/18 // (A61K31/57, 31:54, 31:565), (A61K31/57, 31:535, 31:565), (A61K31/57, 31:495, 31:565), (A61K31/57, 31:41, 31:565)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, SCISEARCH, BIOSIS, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 696 133 A (HAMANN LAWRENCE G ET AL) 9 December 1997 (1997-12-09) claims 1,4,5 ---	1-39
Y	DE 43 30 234 A (SCHERING AG) 9 March 1995 (1995-03-09) column 1, line 1 - line 30 claims 1-8 ---	1-39
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	-/-	
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		<input checked="" type="checkbox"/> Patent family members are listed in annex.
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance		
"E" earlier document but published on or after the international filing date		
"L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention		
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone		
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.		
"&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
21 August 2000		19/09/2000
Name and mailing address of the ISA		Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Bonzano, C

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 521 166 A (GRUBB GARY S) 28 May 1996 (1996-05-28) claim 1 column 2, line 41 - line 60 ----	1-39
Y	US 5 733 902 A (SCHNEIDER MARTIN) 31 March 1998 (1998-03-31) column 1, line 13 - line 19 ----	1-39
Y	DE 43 44 463 A (SCHERING AG) 29 June 1995 (1995-06-29) page 2, line 1 - line 16 -----	1-39

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5,28-39 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Present claims 1,6-27,29-39 relate to a compound defined by reference to a desirable characteristic or property, namely the activity as progestational. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the combination of compounds mentioned in the example 23, with due regard to the general idea underlying the present invention.

Claims searched completely: none.

Claims searched incompletely: 1-39.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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